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<p>(54) Title: ADENO-ASSOCIATED VIRUS SEROTYPE 1 NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME</p> <p>(57) Abstract</p> <p>The nucleic acid sequences of adeno-associated virus (AAV) serotype 1 are provided, as are vectors and host cells containing these sequences and functional fragments thereof. Also provided are methods of delivering genes via AAV-1 derived vectors.</p>			

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ADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID
SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME

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5 this invention.

Field of the Invention

This invention relates generally to viral vector, and more particularly, to recombinant viral vectors useful for gene delivery.

Background of the Invention

10 Adeno-associated viruses are small, single-stranded DNA viruses which require helper virus to facilitate efficient replication [K.I. Berns, *Parvoviridae: the viruses and their replication*, p. 1007-1041, in F.N. Fields et al., Fundamental virology, 3rd ed., vol. 2, (Lippencott-Raven Publishers, Philadelphia, PA) (1995)]. The 4.7 kb genome of AAV is characterized by two inverted terminal repeats (ITR)
15 and two open reading frames which encode the Rep proteins and Cap proteins, respectively. The Rep reading frame encodes four proteins of molecular weight 78 kD, 68 kD, 52 kD and 40 kD. These proteins function mainly in regulating AAV replication and integration of the AAV into a host cell's chromosomes. The Cap reading frame encodes three structural proteins in molecular weight 85 kD (VP 1), 72 kD (VP2) and 61 kD (VP3) [Berns, cited above]. More than 80% of total proteins in
20 AAV virion comprise VP3. The two ITRs are the only *cis* elements essential for AAV replication, packaging and integration. There are two conformations of AAV ITRs called "flip" and "flop". These differences in conformation originated from the replication model of adeno-associated virus which use the ITR to initiate and reinitiate
25 the replication [R.O. Snyder et al., *J. Virol.*, 67:6096-6104 (1993); K.I. Berns, Microbiological Reviews, 54:316-329 (1990)].

AAVs have been found in many animal species, including primates, canine, fowl and human [F.A. Murphy et al., "The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses",

Archives of Virology, (Springer-Verlag, Vienna) (1995)]. In addition to five known primate AAVs (AAV-1 to AAV-5), AAV-6, another serotype closely related to AAV-2 and AAV-1 has also been isolated [E. A. Rutledge et al., J. Virol., 72:309-319 (1998)]. Among all known AAV serotypes, AAV-2 is perhaps the most well-
5 characterized serotype, because its infectious clone was the first made [R.J. Samulski et al., Proc. Natl. Acad. Sci. USA, 79:2077-2081 (1982)]. Subsequently, the full sequences for AAV-3A, AAV-3B, AAV-4 and AAV-6 have also been determined [Rutledge, cited above; J.A. Chiorini et al., J. Virol., 71:6823-6833 (1997); S. Muramatsu et al., Virol., 221:208-217 (1996)]. Generally, all AAVs share more than
10 80% homology in nucleotide sequence.

A number of unique properties make AAV a promising vector for human gene therapy [Muzychka, Current Topics in Microbiology and Immunology, 158:97-129 (1992)]. Unlike other viral vectors, AAVs have not been shown to be associated with any known human disease and are generally not considered pathogenic. Wild type
15 AAV is capable of integrating into host chromosomes in a site specific manner [R. M. Kotin et al., Proc. Natl. Acad. Sci. USA, 87:2211-2215 (1990)- R.J. Samulski, EMBO J., 10(12):3941-3950 (1991)]. Recombinant AAV vectors can integrate into tissue cultured cells in chromosome 19 if the rep proteins are supplied in *trans* [C. Balague et al., J. Virol., 71:3299-3306 (1997); R. T. Suroskey et al., J. Virol., 71:7951-7959 (1997)]. The integrated genomes of AAV have been shown to allow long term gene expression in a number of tissues, including, muscle, liver, and brain
20 [K. J. Fisher, Nature Med., 3(3):306-312 (1997); R. O. Snyder et al., Nature Genetics, 16:270-276 (1997); X. Xiao et al., Experimental Neurology, 144:113-124 (1997); Xiao, J. Virol., 70(11):8098-8108 (1996)].

25 AAV-2 has been shown to be present in about 80-90% of the human population. Earlier studies showed that neutralizing antibodies for AAV-2 are prevalent [W. P. Parks et al., J. Virol., 2:716-722 (1970)]. The presence of such antibodies may significantly decrease the usefulness of AAV vectors based on AAV-2 despite its other merits. What are needed in the art are vectors characterized by the

advantages of AAV-2, including those described above, without the disadvantages, including the presence of neutralizing antibodies.

Summary of the Invention

In one aspect, the invention provides an isolated AAV-1 nucleic acid molecule
5 which is selected from among SEQ ID NO: 1, the strand complementary to SEQ ID NO: 1, and cDNA and RNA sequences complementary to SEQ ID NO: 1 and its complementary strand.

In another aspect, the present invention provides AAV ITR sequences, which include the 5' ITR sequences, nt 1 to 143 of SEQ ID NO: 1; the 3' ITR sequences, nt 10 4576 to 4718 of SEQ ID NO: 1, and fragments thereof.

In yet another aspect, the present invention provides a recombinant vector comprising an AAV-1 ITR and a selected transgene. Preferably, the vector comprises both the 5' and 3' AAV-1 ITRs between which the selected transgene is located.

In still another aspect, the invention provides a recombinant vector comprising 15 an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

In a further aspect, the present invention provides a nucleic acid molecule encoding an AAV-1 rep coding region and an AAV-1 cap coding region.

In still another aspect, the present invention provides a host cell transduced with a 20 recombinant viral vector of the invention. The invention further provides a host cell stably transduced with an AAV-1 P5 promoter of the invention.

In still a further aspect, the present invention provides a pharmaceutical composition comprising a carrier and a vector of the invention.

In yet another aspect, the present invention provides a method for AAV-25 mediated delivery of a transgene to a host involving the step of delivering to a selected host a recombinant viral vector comprising a selected transgene under the control of sequences which direct expression thereof and an adeno-associated virus 1 (AAV-1) virion.

In another aspect, the invention provides a method for in vitro production of a selected gene product using a vector of the invention.

Other aspects and advantages of the invention will be readily apparent to one of skill in the art from the detailed description of the invention.

5 Brief Description of the Drawings

Figs. 1A-1C illustrate the alignment of nucleotides of AAV-1 [SEQ ID NO: 1], AAV-2 [SEQ ID NO: 18] and AAV-6 [SEQ ID NO: 19]. The alignment was done with MacVector 6.0. The full sequences of AAV-1 are shown in the top line. Nucleotides in AAV-2 and AAV-6 identical to AAV-1 are symbolized by "." and gaps 10 by "-". Some of the conserved features among AAVs are marked in this figure. Note the 3' ITRs of AAV-1 and AAV-6 are shown in different orientations.

Fig. 2 illustrates the predicted secondary structure of AAV-1 ITR. The nucleotides in AAV-2 and AAV-6 are shown in italic and bold respectively.

Fig. 3A illustrates a hypothesis of how AAV-6 arose from the homologous 15 recombination between AAV-1 and AAV-2. The major elements of AAV-1 are indicated in the graph. A region that is shared between AAV-1, AAV-2 and AAV-6 is shown in box with waved lines.

Fig. 3B is a detailed illustration of a 71 bp homologous region among AAV-1, AAV-2 and AAV-6. Nucleotides that differ among these serotypes are indicated by 20 arrows.

Fig. 4A is a bar chart illustrating expression levels of human alpha 1 anti-trypsin (α 1AT) in serum following delivery of hAAT via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 4B is a bar chart illustrating expression levels of erythropoietin (epo) in 25 serum following delivery of the *epo* gene via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 5A is a bar chart illustrating expression levels of α 1AT in liver following delivery of α 1AT as described in Example 7.

Fig. 5B is a bar chart demonstrating expression levels of epo in liver following delivery of epo as described in Example 7.

Fig. 5C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to liver as described in Example 7.

5 Fig. 5D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to liver as described in Example 7.

Fig. 6A is a bar chart illustrating expression levels of α 1AT in muscle following delivery of α 1AT as described in Example 7.

10 Fig. 6B is a bar chart demonstrating expression levels of epo in muscle following delivery of epo as described in Example 7.

Fig. 6C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to muscle as described in Example 7.

Fig. 6D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to muscle as described in Example 7.

15 **Detailed Description of the Invention**

The present invention provides novel nucleic acid sequences for an adeno-associated virus of serotype 1 (AAV-1). Also provided are fragments of these AAV-1 sequences. Among particularly desirable AAV-1 fragments are the inverted terminal repeat sequences (ITRs), rep and cap. Each of these fragments may be readily utilized, e.g., as a cassette, in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV-1 sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a cassette may contain the AAV-1 ITRs of the invention flanking a selected transgene. In another desirable embodiment, a cassette may contain the AAV-1 rep and/or cap proteins, e.g., for use in producing recombinant (rAAV) virus.

Thus, the AAV-1 sequences and fragments thereof are useful in production of rAAV, and are also useful as antisense delivery vectors, gene therapy vectors, or vaccine vectors. The invention further provides nucleic acid molecules, gene delivery

vectors, and host cells which contain the AAV-1 sequences of the invention. Also provided a novel methods of gene delivery using AAV vectors.

As described herein, the vectors of the invention containing the AAV-1 capsid proteins of the invention are particularly well suited for use in applications in which 5 the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.

These and other embodiments and advantages of the invention are described in more detail below. As used throughout this specification and the claims, the term 10 "comprising" is inclusive of other components, elements, integers, steps and the like.

I. AAV-1 NUCLEIC ACID AND PROTEIN SEQUENCES

The AAV-1 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 1 (Figs. 1A-1C), which consists of 4718 nucleotides. The AAV-1 nucleic acid sequences of the invention further encompass the strand which is 15 complementary to SEQ ID NO: 1, as well as the RNA and cDNA sequences corresponding to SEQ ID NO: 1 and its complementary strand. Also included in the nucleic acid sequences of the invention are natural variants and engineered modifications of SEQ ID NO: 1 and its complementary strand. Such modifications include, for example, labels which are known in the art, methylation, and substitution 20 of one or more of the naturally occurring nucleotides with an analog.

Further included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 - 99% identical or homologous to SEQ ID NO:1. The term "percent sequence identity" or "identical" in the context of nucleic acid 25 sequences refers to the residues in the two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over the full-length sequence, or a fragment at least about nine nucleotides, usually at least about 20 - 24 nucleotides, at least about 28 - 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different

algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using Fasta, a program in GCG Version 6.1. Fasta provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences 5 (Pearson, 1990, herein incorporated by reference). For instance, percent sequence identity between nucleic acid sequences can be determined using Fasta with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) as provided in GCG Version 6.1, herein incorporated by reference.

The term "substantial homology" or "substantial similarity," when referring to 10 a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95 - 99% of the sequence.

Also included within the invention are fragments of SEQ ID NO: 1, its 15 complementary strand, cDNA and RNA complementary thereto. Suitable fragments are at least 15 nucleotides in length, and encompass functional fragments which are of biological interest. Certain of these fragments may be identified by reference to Figs. 1A-1C. Examples of particularly desirable functional fragments include the AAV-1 inverted terminal repeat (ITR) sequences of the invention. In contrast to the 145 nt 20 ITRs of AAV-2, AAV-3, and AAV-4, the AAV-1 ITRs have been found to consist of only 143 nucleotides, yet advantageously are characterized by the T-shaped hairpin structure which is believed to be responsible for the ability of the AAV-2 ITRs to direct site-specific integration. In addition, AAV-1 is unique among other AAV serotypes, in that the 5' and 3' ITRs are identical. The full-length 5' ITR sequences of 25 AAV-1 are provided at nucleotides 1-143 of SEQ ID NO: 1 (Fig. 1A) and the full-length 3' ITR sequences of AAV-1 are provided at nt 4576-4718 of SEQ ID NO: 1 (Fig. 1C). One of skill in the art can readily utilize less than the full-length 5' and/or 3' ITR sequences for various purposes and may construct modified ITRs using conventional techniques, e.g., as described for AAV-2 ITRs in Samulski et al, Cell, 30 33:135-143 (1983).

Another desirable functional fragment of the AAV-1 genome is the P5 promoter of AAV-1 which has sequences unique among AAV P5 promoters, while maintaining critical regulatory elements and functions. This promoter is located within nt 236 - 299 of SEQ ID NO: 1 (Fig. 1A). Other examples of functional fragments of interest include the sequences at the junction of the rep/cap, e.g., the sequences spanning nt 2306-2223, as well as larger fragments which encompass this junction which may comprise 50 nucleotides on either side of this junction. Still other examples of functional fragments include the sequences encoding the rep proteins. Rep 78 is located in the region of nt 334 - 2306 of SEQ ID NO: 1; Rep 68 is located in the region of nt 334-2272, and contains an intron spanning nt 1924-2220 of SEQ ID NO: 1. Rep 52 is located in the region of nt 1007 - 2304 of SEQ ID NO: 1; rep 40 is located in the region of nt 1007 - 2272, and contains an intron spanning nt 1924-2246 of SEQ ID NO: 1. Also of interest are the sequences encoding the capsid proteins, VP 1 [nt 2223-4431 of SEQ ID NO: 1], VP2 [nt 2634-4432 of SEQ ID NO: 1] and VP3 [nt 2829-4432 of SEQ ID NO: 1]. Other fragments of interest may include the AAV-1 P19 sequences, AAV-1 P40 sequences, the rep binding site, and the terminal resolute site (TRS).

The invention further provides the proteins and fragments thereof which are encoded by the AAV-1 nucleic acids of the invention. Particularly desirable proteins include the rep and cap proteins, which are encoded by the nucleotide sequences identified above. These proteins include rep 78 [SEQ ID NO:5], rep 68 [SEQ ID NO:7], rep 52 [SEQ ID NO:9], rep 40 [SEQ ID NO: 11], vpl [SEQ ID NO: 13], vp2 [SEQ ID NO: 15], and vp3 [SEQ ID NO: 17] and functional fragments thereof while the sequences of the rep and cap proteins have been found to be closely related to those of AAV-6, there are differences in the amino acid sequences (see Table 1 below), as well as differences in the recognition of these proteins by the immune system. However, one of skill in the art may readily select other suitable proteins or protein fragments of biological interest. Suitably, such fragments are at least 8 amino acids in length. However, fragments of other desired lengths may be readily utilized.

Such fragments may be produced recombinantly or by other suitable means, e.g., chemical synthesis.

The sequences, proteins, and fragments of the invention may be produced by any suitable means, including recombinant production, chemical synthesis, or other 5 synthetic means. Such production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

II. VIRAL VECTORS

In another aspect, the present invention provides vectors which utilize the AAV-1 sequences of the invention, including fragments thereof, for delivery of a 10 heterologous gene or other nucleic acid sequences to a target cell. Suitably, these heterologous sequences (i.e., a transgene) encode a protein or gene product which is capable of being expressed in the target cell. Such a transgene may be constructed in the form of a "minigene". Such a "minigene" includes selected heterologous gene sequences and the other regulatory elements necessary to transcribe the gene and 15 express the gene product in a host cell. Thus, the gene sequences are operatively linked to regulatory components in a manner which permit their transcription. Such components include conventional regulatory elements necessary to drive expression of the transgene in a cell containing the viral vector. The minigene may also contain a selected promoter which is linked to the transgene and located, with other regulatory 20 elements, within the selected viral sequences of the recombinant vector.

Selection of the promoter is a routine matter and is not a limitation of this invention. Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the timing and amount of the transgene to be expressed. For example, desirable promoters include the cytomegalovirus (CMV) 25 immediate early promoter/enhancer [see, e.g., Boshart et al, *Cell*, 41:521-530 (1985)], the Rous sarcoma virus LTR promoter/enhancer, and the chicken cytoplasmic β -actin promoter [T. A. Kost et al, *Nucl. Acids Res.*, 11(23):8287 (1983)]. Still other desirable promoters are the albumin promoter and an AAV P5 promoter. Optionally, the selected promoter is used in conjunction with a heterologous enhancer, e.g., the β -

actin promoter may be used in conjunction with the CMV enhancer. Yet other suitable or desirable promoters and enhancers may be selected by one of skill in the art.

The minigene may also desirably contain nucleic acid sequences heterologous to the viral vector sequences including sequences providing signals required for efficient polyadenylation of the transcript (poly-A or pA) and introns with functional splice donor and acceptor sites. A common poly-A sequence which is employed in the exemplary vectors of this invention is that derived from the papovavirus SV-40. The poly-A sequence generally is inserted in the minigene downstream of the transgene sequences and upstream of the viral vector sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV40 T intron sequence. A minigene of the present invention may also contain such an intron, desirably located between the promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional [see, e.g., 15 Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2d edit., Cold Spring Harbor Laboratory, New York (1989) and references cited therein] and many such sequences are available from commercial and industrial sources as well as from Genebank.

The selection of the transgene is not a limitation of the present invention. 20 Suitable transgenes may be readily selected from among desirable reporter genes, therapeutic genes, and optionally, genes encoding immunogenic polypeptides. Examples of suitable reporter genes include β -galactosidase (β -gal), an alkaline phosphatase gene, and green fluorescent protein (GFP). Examples of therapeutic genes include, cytokines, growth factors, hormones, and differentiation factors, 25 among others. The transgene may be readily selected by one of skill in the art. See, e.g., WO 98/09657, which identifies other suitable transgenes.

Suitably, the vectors of the invention contain, at a minimum, cassettes which consist of fragments of the AAV-1 sequences and proteins. In one embodiment, a vector of the invention comprises a selected transgene, which is flanked by a 5' ITR 30 and a 3' ITR, at least one of which is an AAV-1 ITR of the invention. Suitably,

vectors of the invention may contain a AAV-1 P5 promoter of the invention. In yet another embodiment, a plasmid or vector of the invention contains AAV-1 rep sequences. In still another embodiment, a plasmid or vector of the invention contains at least one of the AAV-1 cap proteins of the invention. Most suitably, these AAV-1-derived vectors are assembled into viral vectors, as described herein.

5 A. AAV Viral Vectors

In one aspect, the present invention provides a recombinant AAV-1 viral vector produced using the AAV-1 capsid proteins of the invention. The packaged rAAV-1 virions of the invention may contain, in addition to a selected 10 minigene, other AAV-1 sequences, or may contain sequences from other AAV serotypes.

15 Methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present invention. See, e.g., K. Fisher et al, *J. Virol.*, 70:520-532 (1993) and US Patent 5,478,745. In one suitable method, a selected host cell is provided with the AAV sequence encoding a rep protein, the 20 gene encoding the AAV cap protein and with the sequences for packaging and subsequent delivery. Desirably, the method utilizes the sequences encoding the AAV-1 rep and/or cap proteins of the invention.

In one embodiment, the rep/cap genes and the sequences for delivery 25 are supplied by co-transfection of vectors carrying these genes and sequences. In one currently preferred embodiment, a cis (vector) plasmid, a trans plasmid containing the rep and cap genes, and a plasmid containing the adenovirus helper genes are co-transfected into a suitable cell line, e.g., 293. Alternatively, one or more of these functions may be provided in trans via separate vectors, or may be found in a suitably engineered packaging cell line.

An exemplary cis plasmid will contain, in 5' to 3' order, AAV 5' ITR, the selected transgene, and AAV 3' ITR. In one desirable embodiment, at least one of the AAV ITRs is a 143 nt AAV-1 ITR. However, other AAV serotype ITRs may be readily selected. Suitably, the full-length ITRs are utilized. However, one of skill in

the art can readily prepare modified AAV ITRs using conventional techniques.

Similarly, methods for construction of such plasmids is well known to those of skill in the art.

A trans plasmid for use in the production of the rAAV-1 virion particle 5 may be prepared according to known techniques. In one desired embodiment, this plasmid contains the rep and cap proteins of AAV-1, or functional fragments thereof. Alternatively, the rep sequences may be from another selected AAV serotype.

The cis and trans plasmid may then be co-transfected with a wild-type helper virus (e.g., Ad2, Ad5, or a herpesvirus), or more desirably, a replication - 10 defective adenovirus, into a selected host cell. Alternatively, the cis and trans plasmid may be co-transfected into a selected host cell together with a transfected plasmid which provides the necessary helper functions. Selection of a suitable host cell is well within the skill of those in the art and include such mammalian cells as 293 cells, HeLa cells, among others.

15 Alternatively, the cis plasmid and, optionally the trans plasmid, may be transfected into a packaging cell line which provides the remaining helper functions necessary for production of a rAAV containing the desired AAV-1 sequences of the invention. An example of a suitable packaging cell line, where an AAV-2 capsid is desired, is B-50, which stably expresses AAV-2 rep and cap genes under the control 20 of a homologous P5 promoter. This cell line is characterized by integration into the cellular chromosome of multiple copies (at least 5 copies) of P5-rep-cap gene cassettes in a concatomer form. This B-50 cell line was deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 18, 1997 under Accession No. CRL-12401 pursuant to the 25 provisions of the Budapest Treaty. However, the present invention is not limited as to the selection of the packaging cell line.

Exemplary transducing vectors based on AAV-1 capsid proteins have 30 been tested both *in vivo* and *in vitro*, as described in more detail in Example 4. In these studies, it was demonstrated that recombinant AAV vector with an AAV-1 virion can transduce both mouse liver and muscle. These, and other AAV-1 based

gene therapy vectors which may be generated by one of skill in the art are beneficial for gene delivery to selected host cells and gene therapy patients since the neutralization antibodies of AAV-1 present in much of the human population exhibit different patterns from other AAV serotypes and therefore do not neutralize the

5 AAV-1 virions. One of skill in the art may readily prepare other rAAV viral vectors containing the AAV-1 capsid proteins provided herein using a variety of techniques known to those of skill in the art. One may similarly prepare still other rAAV viral vectors containing AAV-1 sequence and AAV capsids of another serotype.

B. Other Viral Vectors

10 One of skill in the art will readily understand that the AAV-1 sequences of the invention can be readily adapted for use in these and other viral vector systems for *in vitro*, *ex vivo* or *in vivo* gene delivery. Particularly well suited for use in such viral vector systems are the AAV-1 ITR sequences, the AAV-1 rep, the AAV-1 cap, and the AAV-1 P5 promoter sequences.

15 For example, in one desirable embodiment, the AAV-1 ITR sequences of the invention may be used in an expression cassette which includes AAV-1 5' ITR, a non-AAV DNA sequences of interest (e.g., a minigene), and 3' ITR and which lacks functional rep/cap. Such a cassette containing an AAV-1 ITR may be located on a plasmid for subsequent transfection into a desired host cell, such as the cis plasmid 20 described above. This expression cassette may further be provided with an AAV capsid of a selected serotype to permit infection of a cell or stably transfected into a desired host cell for packaging of rAAV virions. Such an expression cassette may be readily adapted for use in other viral systems, including adenovirus systems and lentivirus systems. Methods of producing Ad/AAV vectors are well known to those 25 of skill in the art. One desirable method is described in PCT/US95/14018. However, the present invention is not limited to any particular method.

Another aspect of the present invention is the novel AAV-1 P5 promoter sequences which are located in the region spanning nt 236 - 299 of SEQ ID NO: 1. This promoter is useful in a variety of viral vectors for driving expression of a 30 desired transgene.

Similarly, one of skill in the art can readily select other fragments of the AAV-1 genome of the invention for use in a variety of vector systems. Such vectors systems may include, e.g., lentiviruses, retroviruses, poxviruses, vaccinia viruses, and adenoviral systems, among others. Selection of these vector systems is not a 5 limitation of the present invention.

C. Host Cells And Packaging Cell Lines

In yet another aspect, the present invention provides host cells which may be transiently transfected with AAV-1 nucleic acid sequences of the invention to permit expression of a desired transgene or production of a rAAV particle. For 10 example, a selected host cell may be transfected with the AAV-1 P5 promoter sequences and/or the AAV-1 5' ITR sequences using conventional techniques. Providing AAV helper functions to the transfected cell lines of the invention results in packaging of the rAAV as infectious rAAV particles. Such cell lines may be produced in accordance with known techniques [see, e.g., US Patent No. 5,658,785], making 15 use of the AAV-1 sequences of the invention.

Alternatively, host cells of the invention may be stably transfected with a rAAV expression cassette of the invention, and with copies of AAV-1 rep and cap genes. Suitable parental cell lines include mammalian cell lines and it may be desirable to select host cells from among non-simian mammalian cells. Examples of suitable 20 parental cell lines include, without limitation, HeLa [ATCC CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells. These cell lines are all available from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 USA. Other suitable parent cell lines may be obtained from other sources and may be used to 25 construct stable cell lines containing the P5 and/or AAV rep and cap sequences of the invention.

Recombinant vectors generated as described above are useful for delivery of the DNA of interest to cells.

III. METHODS OF DELIVERING GENES VIA AAV-1 DERIVED VECTORS

In another aspect, the present invention provides a method for delivery of a transgene to a host which involves transfecting or infecting a selected host cell with a recombinant viral vector generated with the AAV-1 sequences (or functional fragments thereof) of the invention. Methods for delivery are well known to those of skill in the art and are not a limitation of the present invention.

In one desirable embodiment, the invention provides a method for AAV-mediated delivery of a transgene to a host. This method involves transfecting or infecting a selected host cell with a recombinant viral vector containing a selected transgene under the control of sequences which direct expression thereof and AAV-1 capsid proteins.

Optionally, a sample from the host may be first assayed for the presence of antibodies to a selected AAV serotype. A variety of assay formats for detecting neutralizing antibodies are well known to those of skill in the art. The selection of such an assay is not a limitation of the present invention. See, e.g., Fisher et al, Nature Med., 3(3):306-312 (March 1997) and W. C. Manning et al, Human Gene Therapy, 9:477-485 (March 1, 1998). The results of this assay may be used to determine which AAV vector containing capsid proteins of a particular serotype are preferred for delivery, e.g., by the absence of neutralizing antibodies specific for that capsid serotype.

In one aspect of this method, the delivery of vector with AAV-1 capsid proteins may precede or follow delivery of a gene via a vector with a different serotype AAV capsid protein. Thus, gene delivery via rAAV vectors may be used for repeat gene delivery to a selected host cell. Desirably, subsequently administered rAAV vectors carry the same transgene as the first rAAV vector, but the subsequently administered vectors contain capsid proteins of serotypes which differ from the first vector. For example, if a first vector has AAV-2 capsid proteins, subsequently administered vectors may have capsid proteins selected from among the other serotypes, including AAV-1, AAV-3A, AAV-3B, AAV-4 and AAV-6.

Thus, a rAAV-1-derived recombinant viral vector of the invention provides an efficient gene transfer vehicle which can deliver a selected transgene to a selected host cell *in vivo or ex vivo* even where the organism has neutralizing antibodies to one or more AAV serotypes. These compositions are particularly well suited to gene 5 delivery for therapeutic purposes. However, the compositions of the invention may also be useful in immunization. Further, the compositions of the invention may also be used for production of a desired gene product *in vitro*.

The above-described recombinant vectors may be delivered to host cells according to published methods. An AAV viral vector bearing the selected transgene 10 may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for 15 this purpose.

The viral vectors are administered in sufficient amounts to transfect the cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse effects, or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts. 20 Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver, oral, intranasal, intravenous, intramuscular, subcutaneous, intradermal, and other parental routes of administration. Routes of administration may be combined, if desired.

Dosages of the viral vector will depend primarily on factors such as the 25 condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective human dosage of the viral vector is generally in the range of from about 1 ml to about 100 ml of solution containing concentrations of from about 1×10^9 to 1×10^{16} genomes virus vector. A preferred human dosage may be about 1×10^{13} to 1×10^{16} AAV genomes. The 30 dosage will be adjusted to balance the therapeutic benefit against any side effects and

such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage resulting in viral vectors, preferably AAV vectors containing the minigene. Optionally, dosage regimens similar to those described for therapeutic purposes may be utilized for immunization using the compositions of the invention. For *in vitro* production, a desired protein may be obtained from a desired culture following transfection of host cells with a rAAV containing the gene encoding the desired protein and culturing the cell culture under conditions which permits expression. The expressed protein may then be purified and isolated, as desired. Suitable techniques for transfection, cell culturing, purification, and isolation are known to those of skill in the art.

The following examples illustrate several aspects and embodiments of the invention.

Example 1 - Generation of Infectious Clone of AAV-1

15 The replicated form DNA of AAV-1 was extracted from 293 cells that were infected by AAV-1 and wild type adenovirus type 5.

A. Cell Culture and Virus

AAV-free 293 cells and 84-31 cells were provided by the human application laboratory of the University of Pennsylvania. These cells were cultured in 20 Dulbecco's Modified Eagle Medium with 10% fetal bovine serum (Hyclone), penicillin (100 U/ml) and streptomycin at 37°C in a moisturized environment supplied with 5% CO₂. The 84-31 cell line constitutively expresses adenovirus genes E1a, E1b, E4/ORF6, and has been described previously [K. J. Fisher, J. Virol., **70**:520-532 (1996)]. AAV-1 (ATCC VR-645) seed stock was purchased from American Type 25 Culture Collection (ATCC, Manassas, VA). AAV viruses were propagated in 293 cells with wild type Ad5 as a helper virus.

B. Recombinant AAV Generation

The recombinant AAV viruses were generated by transfection using an adenovirus free method. Briefly, the cis plasmid (with AAV ITR), trans plasmid (with

AAV rep gene and cap gene) and helper plasmid (pF_Δ13, with essential regions from the adenovirus genome) were simultaneously co-transfected into 293 cells in a ratio of 1:1:2 by calcium phosphate precipitation. The pF_Δ13 helper plasmid has an 8 kb deletion in the adenovirus E2B region and has deletions in most of the late genes.

5 This helper plasmid was generated by deleting the RsrII fragment from pFG140 (Microbix, Canada). Typically, 50 µg of DNA (cis:trans:pF_Δ13 at ratios of 1:1:2, respectively) was transfected onto a 15 cm tissue culture dish. The cells were harvested 96 hours post-transfection, sonicated and treated with 0.5% sodium deoxycholate (37°C for 10 min). Cell lysates were then subjected to two rounds of a
10 CsCl gradient. Peak fractions containing AAV vector were collected, pooled, and dialyzed against PBS before injecting into animals. To make rAAV virus with AAV-1 virion, the pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide rep and cap function.

For the generation of rAAV based on AAV-2, p5E18 was used as the
15 *trans* plasmid since it greatly improved the rAAV yield. This plasmid, p5E18(2/2), expresses AAV-2 Rep and Cap and contains a P5 promoter relocated to a position 3' to the Cap gene, thereby minimizing expression of Rep78 and Rep68. The strategy was initially described by Li et al, *J. Virol.*, 71:5236-5243 (1997). P5E18(2/2) was constructed in the following way. The previously described pMMTV-trans vector
20 (i.e., the mouse mammary tumor virus promoter substituted for the P5 promoter in an AAV-2-based vector) was digested with *Sma*I and *Clal*, filled in with the Klenow enzyme, and then recircularized with DNA ligase. The resulting construct was digested with *Xba*I, filled in, and ligated to the blunt-ended *Bam*HI-*Xba*I fragment from pCR-p5, constructed in the following way. The P5 promoter of AAV was amplified by PCR and the amplified fragment was subsequently cloned into pCR2.1
25 (Invitrogen) to yield pCR-P5. The helper plasmid pAV1H was constructed by cloning the *Bfa*I fragment of pAAV-2 into pBluescript II-SK(+) at the *Bcor*V and *Sma*I sites. The 3.0-kb *Xba*I-*Kpn*I fragment from p5E18(2/2), the 2.3-kb *Xba*I-*Kpn*I fragment from pAV1H, and the 1.7-kb *Kpn*I fragment from p5E18(2/2) were incorporated into
30 a separate plasmid P5E18(2/1), which contains AAV-2 Rep, AAV-1 Cap, and the

AAV-2 P5 promoter located 3' to the Cap gene. Plasmid p5E18(2/1) produced 10- to 20-fold higher quantities of the vector than pAV1H (i.e., 10^{12} genomes/50 15-cm² plates).

5 C. DNA Techniques

Hirt DNA extraction was performed as described in the art with minor modification [R.J. Samulski et al., *Cell*, 33:135-143 (1983)]. More particularly, Hirst solution without SDS was used instead of using original Hirt solution containing SDS. The amount of SDS present in the original Hirst solution was added after the cells had been fully suspended. To construct AAV-1 infectious clone, the Hirt DNA from 10 AAV-1 infected 293 cells was repaired with Klenow enzyme (New England Biolabs) to ensure the ends were blunt. The treated AAV-1 Hirt DNA was then digested with *BamHI* and cloned into three vectors, respectively. The internal *BamHI* was cloned into pBlueScript II-SK+ cut with *BamHI* to get pAV1-BM. The left and right fragments were cloned into pBlueScript II-SK+ cut with *BamHI* + *EcoRV* to obtain 15 pAV1-BL and pAV1-BR, respectively. The AAV sequence in these three plasmids were subsequently assembled into the same vector to get AAV-1 infectious clone pAAV-1. The helper plasmid for recombinant AAV-1 virus generation was constructed by cloning the *Bfa I* fragment of pAAV-1 into pBlueScript II-SK+ at the *EcoRV* site.

20 Analysis of the Hirt DNA revealed three bands, a dimer at 9.4 kb, a monomer at 4.7 kb and single-stranded DNA at 1.7 kb, which correlated to different replication forms of AAV-1. The monomer band was excised from the gel and then digested with *BamHI*. This resulted in three fragments of 1.1 kb, 0.8 kb and 2.8 kb. This pattern is in accordance with the description by Bantel-schaal and zur Hausen, 25 *Virol.*, 134(1):52-63 (1984). The 1.1 kb and 2.8 kb *BamHI* fragments were cloned into pBlueScript-KS(+) at *BamHI* and *EcoRV* site. The internal 0.8 kb fragment was cloned into *BamHI* site of pBlueScript-KS(+).

These three fragments were then subcloned into the same construct to obtain a plasmid (pAAV-1) that contained the full sequence of AAV-1. The pAAV-1 30 was then tested for its ability to rescue from the plasmid backbone and package

infectious virus. The pAAV-1 was then transfected to 293 cells and supplied with adenovirus type as helper at MOI 10. The virus supernatant was used to reinfect 293 cells.

For Southern blot analysis, Hirt DNA was digested with *Dpn*I to remove bacteria-borne plasmid and probed with internal *Bam*HI fragment of AAV-1. The membrane was then washed at high stringency conditions, which included: twice 30 minutes with 2X SSC, 0.1% SDS at 65°C and twice 30 minutes with 0.1X SSC, 0.1% SDS at 65°C. The membrane was then analyzed by both phosphor image and X-ray autoradiography. The results confirmed that pAAV-1 is indeed an infectious clone of AAV serotype 1.

Example 2 - Sequencing Analysis of AAV-1

The entire AAV-1 genome was then determined by automatic sequencing and was found to be 4718 nucleotides in length (Figs. 1A-1C). For sequencing, an ABI 373 automatic sequencer as used to determine the sequences for all plasmids and PCR fragments related to this study using the FS dye chemistry. All sequences were confirmed by sequencing both plus and minus strands. These sequences were also confirmed by sequencing two independent clones of pAV-BM, pAV-BL and pAV-BR. Since the replicated form of AAV-1 DNA served as the template for sequence determination, these sequences were also confirmed by sequencing a series of PCR products using original AAV-1 seed stock as a template.

The length of AAV-1 was found to be within the range of the other serotypes: AAV-3 (4726 nucleotides), AAV-4 (4774 nucleotides), AAV-2 (4681 nucleotides), and AAV-6 (4683 nucleotides).

The AAV-1 genome exhibited similarities to other serotypes of adeno-associated viruses. Overall, it shares more than 80% identity with other known AAV viruses as determined by the computer program Megalign using default settings [DNASTAR, Madison, WI]. The key features in AAV-2 can also be found in AAV-1. First, AAV-1 has the same type of inverted terminal repeat which is capable of forming T-shaped hairpin structures, despite the differences at the nucleotide level

(Figs. 2 and 3). The sequences of right ITRs and left ITRs of AAV-1 are identical. The AAV TR sequence is subdivided into A, A', B, B', C, C', D and D' [Bern, cited above].

These AAV ITR sequences are also virtually the same as those found in AAV-5 6 right ITR, there being one nucleotide difference in each of A and A' sequence, and the last nucleotide of the D sequence. Second, the AAV-2 rep binding motif [GCTCGCTCGCTCGCTG (SEQ ID NO: 20)] is well conserved. Such motif can also be found in the human chromosome 19 AAV-2 pre-integration region. Finally, non-structural and structural coding regions, and regulatory elements similar to those 10 of other AAV serotypes also exist in AAV-1 genome.

Although the overall features of AAV terminal repeats are very much conserved, the total length of the AAV terminal repeat exhibits divergence. The terminal repeat of AAV-1 consists of 143 nucleotides while those of AAV-2, AAV-3, and AAV-4 are about 145 or 146 nucleotides. The loop region of AAV-1 ITR most 15 closely resembles that of AAV-4 in that it also uses TCT instead of the TTT found in AAV-2 and AAV-3. The possibility of sequencing error was eliminated using restriction enzyme digestion, since these three nucleotides are part of the SacI site (gagctc; nt 69-74 of SEQ ID NO: 1). The p5 promoter region of AAV-1 shows more variations in nucleotide sequences with other AAV serotypes. However, it still 20 maintains the critical regulatory elements. The two copies of YY1 [See, Fig. 1A-1C] sites seemed to be preserved in all known AAV serotypes, which have been shown to be involved in regulating AAV gene expression. In AAV-4, there are 56 additional nucleotides inserted between YY1 and E-box/USF site, while in AAV-1, there are 26 additional nucleotides inserted before the E-box/USF site. The p19 promoter, p40 25 promoter and polyA can also be identified from the AAV-1 genome by analogy to known AAV serotypes, which are also highly conserved.

Thus, the analysis of AAV terminal repeats of various serotypes showed that the A and A' sequence is very much conserved. One of the reasons may be the Rep binding motif (GCTC),GCTG [SEQ ID NO: 20]. These sequences appear to be 30 essential for AAV DNA replication and site-specific integration. The same sequence

has also been shown to be preserved in a monkey genome [Samulski, personal communication]. The first 8 nucleotides of the D sequence are also identical in all known AAV serotypes. This is in accordance with the observation of the Srivastava group that only the first 10 nucleotides are essential for AAV packaging [X.S. Wang 5 et al, *J. Virol.*, **71**:3077-3082 (1997); X.S. Wang et al, *J. Virol.*, **71**:1140-1146 (1997)]. The function of the rest of the D sequences still remain unclear. They may be somehow related to their tissue specificities. The variation of nucleotide in B and C sequence may also suggest that the secondary structure of the ITRs is more critical for its biological function, which has been demonstrated in many previous 10 publications.

Example 3 - Comparison of AAV-1 Sequences

The nucleotide sequences of AAV-1, obtained as described above, were compared with known AAV sequences, including AAV-2, AAV-4 and AAV-6 using DNA Star Megalign. This comparison revealed a stretch of 71 identical nucleotides 15 shared by AAV-1, AAV-2 and AAV-6. See, Figs. 1A-1C.

This comparison further suggested that AAV-6 is a hybrid formed by homologous recombination of AAV-1 and AAV-2. See, Figs. 3A and 3B. These 20 nucleotides divide the AAV-6 genome into two regions. The 5' half of AAV-6 of 522 nucleotides is identical to that of AAV-2 except in 2 positions. The 3' half of AAV-6 including the majority of the rep gene, complete cap gene and 3' ITR is 98% identical to AAV-1.

Biologically, such recombination may enable AAV-1 to acquire the ability to transmit through the human population. It is also interesting to note that the ITRs of AAV-6 comprise one AAV-1 ITR and one AAV-2 ITR. The replication model of 25 defective parvovirus can maintain this special arrangement. Studies on AAV integration have shown that a majority of AAV integrants carries deletions in at least one of the terminal repeats. These deletions have been shown to be able to be repaired through gene conversion using the other intact terminal repeat as a template. Therefore, it would be very difficult to maintain AAV-6 as a homogenous population

when an integrated copy of AAV-6 is rescued from host cells with helper virus infection. The AAV-6 with two identical AAV-2 ITRs or two identical AAV-1 ITRs should be the dominant variants. The AAV-6 with two AAV-1 ITRs has been observed by Russell's group [Rutledge, cited above (1998)]. So far there is no report 5 on AAV-6 with two AAV-2 ITRs. Acquisition of AAV-2 P5 promoter by AAV-6 may have explained that AAV-6 have been isolated from human origin while AAV-1 with the same virion has not. The regulation of P5 promoter between different species of AAV may be different *in vivo*. This observation suggests the capsid proteins of AAV were not the only determinants for tissue specificity.

10 Although it is clear that AAV-6 is a hybrid of AAV-1 and AAV-2, AAV-6 has already exhibited divergence from either AAV-1 or AAV-2. There are two nucleotide differences between AAV-6 and AAV-2 in their first 450 nucleotides. There are about 1% differences between AAV-6 and AAV-1 in nucleotide levels from nucleotides 522 to the 3' end. There also exists a quite divergent region (nucleotide 15 4486-4593) between AAV-6 and AAV-1 (Figs. 1A-1C). This region does not encode any known proteins for AAVs. These differences in nucleotide sequences may suggest that AAV-6 and AAV-1 have gone through some evolution since the recombination took place. Another possible explanation is that there exists another variant of AAV-1 which has yet to be identified. So far, there is no evidence to rule 20 out either possibility. It is still unknown if other hybrids (AAV-2 to AAV-4, etc.) existed in nature.

The coding region of AAV-1 was deduced by comparison with other known AAV serotypes. Table 1 illustrates the coding region differences between AAV-1 and AAV-6. The amino acid residues are deduced according to AAV-2.

25 With reference to the amino acid position of AAV-1, Table 1 lists the amino acids of AAV-1 which have been changed to the corresponding ones of AAV-6. The amino acids of AAV-1 are shown to the left of the arrow. Reference may be made to SEQ ID NO: 5 of the amino acid sequence of AAV-1 Rep 78 and to SEQ ID NO: 13 for the amino acid sequence of AAV-1 VP1.

Table 1

Coding region variations between AAV-1 and AAV-6

5

Rep protein (Rep78)		Cap protein (VP1)	
Position(s)	Amino acids	Position(s)	Amino acids
28	S-N	129	L-F
191	Q-H		E-D
192	H-D		E-K
308	E-D		F-L
			A-V
			N-H

It was surprising to see that the sequence of the AAV-1 coding region is
10 almost identical to that of AAV-6 from position 452 to the end of coding region (99%). The first 508 nucleotides of AAV-6 have been shown to be identical to those of AAV-2 [Rutledge, cited above (1998)]. Since the components of AAV-6 genome seemed to be AAV-2 left ITR – AAV-2 p5 promoter – AAV-1 coding region – AAV-1 right ITR, it was concluded that AAV-6 is a naturally occurred hybrid between
15 AAV-1 and AAV-2.

Example 4 - Gene Therapy Vector Based on AAV-1

Recombinant gene transfer vectors based on AAV-1 viruses were constructed by the methods described in Example 1. To produce a hybrid recombinant virus with AAV-1 virion and AAV-2 ITR, the AAV-1 trans plasmid (pAV1H) and the AAV-2 cis-lacZ plasmid (with AAV-2 ITR) were used. The AAV-2 ITR was used in this vector in view of its known ability to direct site-specific integration. Also constructed for use in this experiment was an AAV-1 vector carrying the green fluorescent protein (GFP) marker gene under the control of the immediate early promoter of CMV using pAV1H as the trans plasmid.

A. rAAV-1 Viruses Transfect Host Cells in Vitro

84-31 cells, which are subclones of 293 cells (which express adenovirus E1a, E1b) which stably express E4/ORF5, were infected with rAAV-1 GFP or rAAV-lacZ. High levels of expression of GFP and lacZ was detected in the 5 cultured 84-31 cells. This suggested that rAAV-1 based vector was very similar to AAV-2 based vectors in ability to infect and expression levels.

B. rAAV-1 Viruses Transfect Cells in Vivo

The performance of AAV-1 based vectors was also tested *in vivo*. The rAAV-1 CMV- α 1AT virus was constructed as follows. The EcoRI fragment of 10 pAT85 (ATCC) containing human α 1-antitrypsin (α 1AT) cDNA fragment was blunted and cloned into PCR (Promega) at a SmaI site to obtain PCR- α 1AT. The CMV promoter was cloned into PCR- α 1AT at the XbaI site. The Alb- α 1AT expression cassette was removed by XhoI and ClaI and cloned into pAV1H at the XbaI site. This vector plasmid was used to generate AAV-1-CMV- α 1AT virus used 15 in the experiment described below.

For screening human antibodies against AAV, purified AAV virus is lysed with Ripa buffer (10 mM Tris pH 8.2, 1% Triton X-100, 1% SDS, 0.15 M NaCl) and separated in 10% SDS-PAGE gel. The heat inactivated human serum was used at a 1 to 1000 dilution in this assay. The rAAV-1 CMV- α 1AT viruses were 20 injected into Rag-1 mice through tail vein injection at different dosages. The concentration of human α 1-antitrypsin in mouse serum was measured using ELISA. The coating antibody is rabbit anti-human human α 1-antitrypsin (Sigma). The goat-antihuman α 1-antitrypsin (Sigma) was used as the primary detection antibodies. The sensitivity of this assay is around 0.3 ng/ml to 30 ng/ml. The expression of human α -antitrypsin in mouse blood can be detected in a very encouraging level. This result is 25 shown in Table 2.

Table 2

Human Antitrypsin Expressed in Mouse Liver

Amount of virus injected	Week 2 (ng/ml)	Week 4 (ng/ml)
2×10^{10} genomes	214.2	171.4
1×10^{10} genomes	117.8	109.8
5×10^{10} genomes	64.5	67.8
2.5×10^{10} genomes	30.9	58.4

5

10

rAAV-1 CMV-lacZ viruses were also injected into the muscle of C57BL6 mice and similar results were obtained. Collectively, these results suggested that AAV-1 based vector would be appropriate for both liver and muscle gene delivery.

Example 5 - Neutralizing Antibodies Against AAV-1

15

Simple and quantitative assays for neutralizing antibodies (NAB) to AAV-1 and AAV-2 were developed with recombinant vectors. A total of 33 rhesus monkeys and 77 normal human subjects were screened.

A. *Nonhuman Primates*

20

Wild-caught juvenile rhesus monkeys were purchased from Covance (Alice, Tex.) and LABS of Virginia (Yemassee, SC) and kept in full quarantine. The monkeys weighed approximately 3 to 4 kg. The nonhuman primates used in the Institute for Human Gene Therapy research program are purposefully bred in the United States from specific-pathogen-free closed colonies. All vendors are US Department of Agriculture class A dealers. The rhesus macaques are therefore not infected with important simian pathogens, including the tuberculosis agent, major simian lentiviruses (simian immunodeficiency virus and simian retroviruses), and cercopithecine herpesvirus. The animals are also free of internal and external parasites. The excellent health status of these premium animals minimized the potential for extraneous variables. For this study, serum was obtained from monkeys prior to initiation of any protocol.

25

NAB titers were analyzed by assessing the ability of serum antibody to inhibit the transduction of reporter virus expressing green fluorescent protein (GFP) (AAV1-GFP or AAV2-GFP) into 84-31 cells. Various dilutions of antibodies preincubated with reporter virus for 1 hour at 37°C were added to 90% confluent cell cultures. Cells were incubated for 48 hours and the expression of green fluorescent protein was measured by FluoroImaging (Molecular Dynamics). NAB titers were calculated as the highest dilution at which 50% of the cells stained green.

Analysis of NAB in rhesus monkeys showed that 61% of animals tested positive for AAV-1; a minority (24%) has NAB to AAV-2. Over one-third of animals had antibodies to AAV-1 but not AAV-2 (i.e., were monospecific for AAV-1), whereas no animals were positive for AAV-2 without reacting to AAV-1. These data support the hypothesis that AAV-1 is endemic in rhesus monkeys. The presence of true AAV-2 infections in this group of nonhuman primates is less clear, since cross-neutralizing activity of an AAV-1 response to AAV-2 can not be ruled out. It is interesting that there is a linear relationship between AAV-2 NAB and AAV-1 NAB in animals that had both.

B. Humans

For these neutralization antibody assays, human serum samples were incubated at 56°C for 30 min to inactivate complement and then diluted in DMEM. The virus (rAAV or rAd with either lacZ or GFP) was then mixed with each serum dilution (20X, 400X, 2000X, 4000X, etc.) and incubated for 1 hour at 37°C before applied to 90% confluent cultures of 84-31 cells (for AAV) or Hela cells (for adenovirus) in 96-well plates. After 60 minutes of incubation at culture condition, 100 µl additional media containing 20% FCS was added to make final culture media containing 10% FCS.

The result is summarized in Table 3.

Table 3

Adenovirus	AAV-1	AAV-2	# of samples	Percentage
5	-	-	41	53.2%
	+	-	16	20.8%
	-	+	0	0.0%
	-	+	2	2.6%
	-	+	2	2.6%
10	+	-	3	3.9%
	+	+	0	0.0%
	+	+	13	16.9%
	Total		77	100%

The human neutralizing antibodies against these three viruses seemed to be unrelated since the existence of neutralizing antibodies against AAV are not indications for antibodies against adenovirus. However, AAV requires adenovirus as helper virus, in most of the cases, the neutralizing antibodies against AAV correlated with the existence of neutralizing antibodies to adenovirus. Among the 77 human serum samples screened, 41% of the samples can neutralize the infectivity of recombinant adenovirus based on Ad5. 15/77 (19%) of serum samples can neutralize the transduction of rAAV-1 while 20/77 (20%) of the samples inhibit rAAV-2 transduction at 1 to 80 dilutions or higher. All serum samples positive in neutralizing antibodies for AAV-1 are also positive for AAV-2. However, there are five (6%) rAAV-2 positive samples that failed to neutralize rAAV-1. In samples that are positive for neutralizing antibodies, the titer of antibodies also varied in the positive ones. The results from screening human sera for antibodies against AAVs supported the conclusion that AAV-1 presents the same epitome as that of AAV-2 to interact

with cellular receptors since AAV-1 neutralizing human serums can also decrease the infectivity of AAV-2. However, the profile of neutralizing antibodies for these AAVs is not identical, there are additional specific receptors for each AAV serotype.

Example 6 - Recombinant AAV Viruses Exhibit Tissue Tropism

5 The recombinant AAV-1 vectors of the invention and the recombinant AAV-2 vectors [containing the gene encoding human α 1-antitrypsin (α 1AT) or murine erythropoietin (Epo) from a cytomegalovirus-enhanced β -actin promoter (CB)] were evaluated in a direct comparison to equivalent copies of AAV-2 vectors containing the same vector genes.

10 Recombinant viruses with AAV-1 capsids were constructed using the techniques in Example 1. To make rAAV with AAV-1 virions, pAV1H or pSE18 (2/1) was used as the *trans* plasmid to provide Rep and Cap functions. For the generation of the rAAV based on AAV-2, pSE18(2/2) was used as the *trans* plasmid, since it greatly improved the rAAV yield. [Early experiments indicated similar *in vivo* performances of AAV-1 vectors produced with pAV1H and pSE19 (2/1). All subsequent studies used AAV-1 vectors derived from pSE18(2/1) because of the increased yield.]

15 Equivalent stocks of the AAV-1 and AAV-2 vectors were injected intramuscularly (5×10^{10} genomes) or liver via the portal circulation (1×10^{11} genomes) into immunodeficient mice, and the animals (four groups) were analyzed on day 30 for expression of transgene. See, Figs. 4A and 4B.

20 AAV-2 vectors consistently produced 10- to 50-fold more serum erythropoietin or α 1-antitrypsin when injected into liver compared to muscle. (However, the AAV-1-delivered genes did achieve acceptable expression levels in the liver.) This result was very different from that for AAV-1 vectors, with which muscle expression was equivalent to or greater than liver expression. In fact, AAV-1 outperformed AAV-2 in muscle when equivalent titers based on genomes were administered.

Example 7 - Gene Delivery via rAAV-1

C57BL/6 mice (6- to 8-week old males, Jackson Laboratories) were analyzed for AAV mediated gene transfer to liver following intrasplenic injection of vector (i.e., targeted to liver). A total of 10^{11} genome equivalents of rAAV-1 or rAAV-2 vector were injected into the circulation in 100 μ l buffered saline. The first vector contained either an AAV-1 capsid or an AAV-2 capsid and expressed α 1AT under the control of the chicken β -actin (CB) promoter. Day 28 sera were analyzed for antibodies against AAV-1 or AAV-2 and serum α 1AT levels were checked. Animals were then injected with an AAV-1 or AAV-2 construct expressing erythropoietin (Epo, also under the control of the CB promoter). One month later sera was analyzed for serum levels of Epo. The following groups were analyzed (Figs. 5A-5D).

In Group 1, vector 1 was AAV-2 expressing α 1AT and vector 2 was AAV-2 expressing Epo. Animals generated antibodies against AAV-2 following the first vector administration which prevented the readministration of the AAV-2 based vector. There was no evidence for cross-neutralizing the antibody to AAV-1.

In Group 2, vector 1 was AAV-1 expressing α 1AT while vector 2 was AAV-1 expressing Epo. The first vector administration did result in significant α 1AT expression at one month associated with antibodies to neutralizing antibodies to AAV-1. The animals were not successfully readministered with the AAV-1 Epo expressing construct.

In Group 3, the effectiveness of an AAV-2 vector expressing Epo injected into a naive animal was measured. The animals were injected with PBS and injected with AAV-2 Epo vector at day 28 and analyzed for Epo expression one month later. The neutralizing antibodies were evaluated at day 28 so we did not expect to see anything since they received PBS with the first vector injection. This shows that in naive animals AAV-2 is very efficient at transferring the Epo gene as demonstrated by high level of serum Epo one month later.

Group 4 was an experiment similar to Group 3 in which the animals originally received PBS for vector 1 and then the AAV-1 expressing Epo construct 28 days later. At the time of vector injection, there obviously were no antibodies to either

AAV-1 or AAV-2. The AAV-1 based vector was capable of generating significant expression of Epo when measured one month later.

Group 5 is a cross-over experiment where the initial vector is AAV-2 expressing α 1AT followed by the AAV-1 construct expressing Epo. The animals, as 5 expected, were efficiently infected with the AAV-2 vector expressing α 1AT as shown by high levels of the protein in blood at 28 days. This was associated with significant neutralizing antibodies to AAV-2. Importantly, the animals were successfully administered AAV-1 following the AAV-2 vector as shown by the presence of Epo in serum 28 days following the second vector administration. At the time of this vector 10 administration, there was high level AAV-2 neutralizing antibodies and very low cross-reaction to AAV-1. The level of Epo was slightly diminished possibly due to a small amount of cross-reactivity. Group 6 was the opposite cross-over experiment in which the initial vector was AAV-1 based, whereas the second experiment was AAV-2 based. The AAV-1 vector did lead to significant gene expression of α 1AT, which 15 also resulted in high level AAV-1 neutralizing antibody. The animals were very efficiently administered AAV-2 following the initial AAV-1 vector as evidenced by high level Epo.

A substantially identical experiment was performed in muscle in which 5×10^{10} genomes were injected into the tibialis anterior of C57BL/6 mice as a model for 20 muscle directed gene therapy. The results are illustrated in Figs. 6A-6D and are essentially the same as for liver.

In summary, this experiment demonstrates the utility of using an AAV-1 vector in patients who have pre-existing antibodies to AAV-2 or who had initially received an AAV-2 vector and need readministration.

25 Example 8 - Construction of Recombinant Viruses Containing AAV-1 ITRs

This example illustrates the construction of recombinant AAV vectors which contain AAV-1 ITRs of the invention.

An AAV-1 cis plasmid is constructed as follows. A 160 bp Xho-NruI AAV-1 fragment containing the AAV-1 5' ITR is obtained from pAV1-BL. pAV1-BL was

generated as described in Example 1. The Xho-NruI fragment is then cloned into a second pAV1-BL plasmid at an XbaI site to provide the plasmid with two AAV-1 ITRs. The desired transgene is then cloned into the modified pAV-1BL at the NruI and BamHI site, which is located between the AAV-1 ITR sequences. The resulting 5 AAV-1 cis plasmid contains AAV-1 ITRs flanking the transgene and lacks functional AAV-1 rep and cap.

Recombinant AAV is produced by simultaneously transfecting three plasmids into 293 cells. These include the AAV-1 cis plasmid described above; a trans plasmid which provides AAV rep/cap functions and lacks AAV ITRs; and a plasmid providing 10 adenovirus helper functions. The rep and/or cap functions may be provided in trans by AAV-1 or another AAV serotype, depending on the immunity profile of the intended recipient. Alternatively, the rep or cap functions may be provided in cis by AAV-1 or another serotype, again depending on the patient's immunity profile.

In a typical cotransfection, 50 µg of DNA (cis:trans:helper at ratios of 1:1:2, 15 respectively) is transfected onto a 15 cm tissue culture dish. Cells are harvested 96 hours post transfection; sonicated and treated with 0.5% sodium deoxycholate (37° for 10 min). Cell lysates are then subjected to 2-3 rounds of ultracentrifugation in a cesium gradient. Peak fractions containing rAAV are collected, pooled and dialyzed against PBS. A typical yield is 1×10^{13} genomes/10⁹ cells.

20 Using this method, one recombinant virus construct is prepared which contains the AAV-1 ITRs flanking the transgene, with an AAV-1 capsid. Another recombinant virus construct is prepared with contains the AAV-1 ITRs flanking the transgene, with an AAV-2 capsid.

All publications cited in this specification are incorporated herein by reference. 25 While the invention has been described with reference to a particularly preferred embodiments, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the claims.

What is claimed is:

1. An isolated AAV-1 nucleic acid molecule comprising a sequence selected from the group consisting of:

- (a) SEQ ID NO: 1;
- (b) a DNA sequence complementary to SEQ ID NO: 1;
- (c) cDNA complementary to (a) or (b); and
- (d) RNA complementary to any of (a) to (c).

2. A nucleic acid molecule comprising an AAV-1 inverted terminal repeat (ITR) sequence selected from the group consisting of:

- (a) nt 1 to 143 of SEQ ID NO: 1;
- (b) nt 4576 to 4718 of SEQ ID NO: 1;
- (c) a nucleic acid sequence complementary to (a) or (b); and
- (d) a functional fragment of (a), (b), or (c).

3. A recombinant vector comprising a 5' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 1 to 143 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

4. The recombinant vector according to claim 3, wherein said vector further comprises a 3' AAV-1 ITR.

5. A recombinant vector comprising a 3' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 4576 to 4718 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

6. The recombinant vector according to claim 5, wherein said vector further comprises a 5' AAV-1 ITR.

7. The recombinant vector according to any of claims 3-6, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.

8. The recombinant vector according to any of claims 3-6, wherein said vector further comprises adenovirus sequences.

9. A recombinant vector comprising an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

10. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said cap coding region comprises at least one member selected from the group consisting of:

- (a) vp1, nt 2223 to 4431 of SEQ ID NO: 1;
- (b) vp2, nt 2634 to 4432 of SEQ ID NO: 1; and
- (c) vp3, nt 2829 to 4432 of SEQ ID NO: 1.

11. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said rep coding region comprises an AAV-1 rep coding region comprising at least one member selected from the group consisting of:

- (a) rep 78, nt 335 to 2304 of SEQ ID NO: 1;
- (b) rep 68, nt 335 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto;
- (c) rep 52, nt 1007 to 2304 of SEQ ID NO: 1; and
- (d) rep 40, nt 1007 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto.

12. A host cell transduced with a recombinant viral vector according to any of claims 3-6.

13. A host cell transduced with a nucleic acid molecule according to any of claims 1, 2, 10 or 11.

14. A host cell stably transduced with an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1.

15. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to any of claims 3-6.

16. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 7.

17. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 8.

18. A method for AAV-mediated delivery of a transgene comprising the step of delivering to a host cell an AAV virion which comprises:

- (a) a capsid comprising at least one capsid protein encoded by an AAV-1 cap gene; and
- (b) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

19. A method for AAV-mediated delivery of a transgene to a host comprising the steps of:

- (a) assaying a sample from the host to determine the presence of neutralizing antibodies specific against any serotype of AAV; and
- (b) delivering to the host an AAV virion which comprises:
 - (i) a capsid comprising at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has no antibodies as determined in step (a); and
 - (ii) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

20. The method according to claim 19, comprising the additional step of repeating steps (a) and (b).

21. Use of an AAV virion which comprises a capsid comprising (a) at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has antibodies, and (b) a DNA molecule comprising a transgene operably linked to regulatory sequences directing its expression,

in the preparation of a medicament for delivery of a transgene to a host, wherein said host has no preexisting neutralizing antibodies against the AAV serotype of said cap gene.

22. A method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to any of claims 3-8.

23. A method for producing a selected gene product comprising the steps of transfecting a mammalian cell with the molecule according to claim 1 or a functional fragment thereof and culturing said cell under conditions suitable to express said gene product.

FIG 1A

FIG. 18

FIG 1C

AAV-1 TR

FIG 2

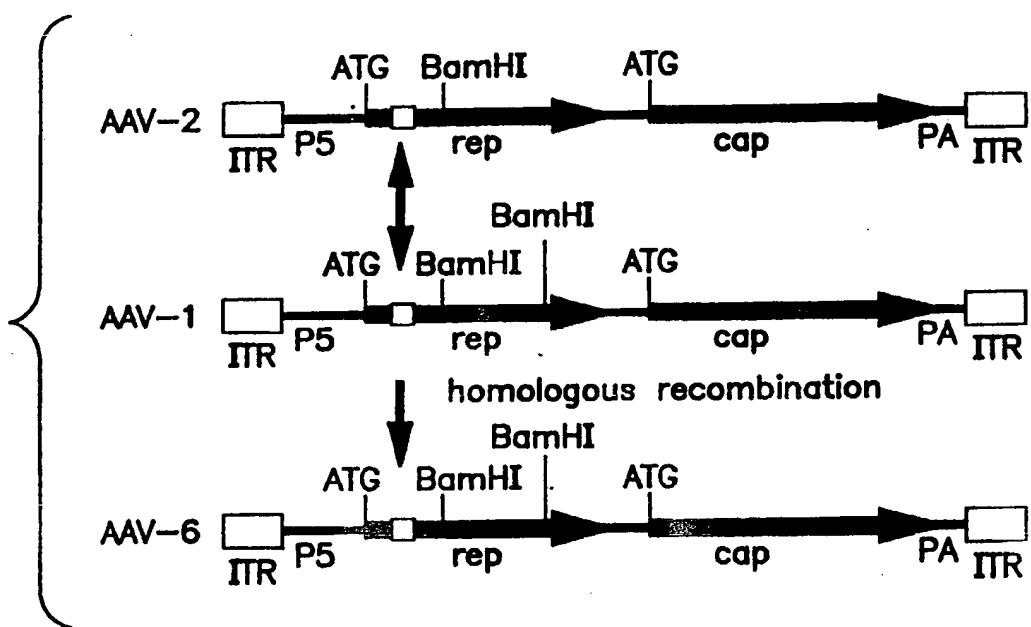


FIG. 3A

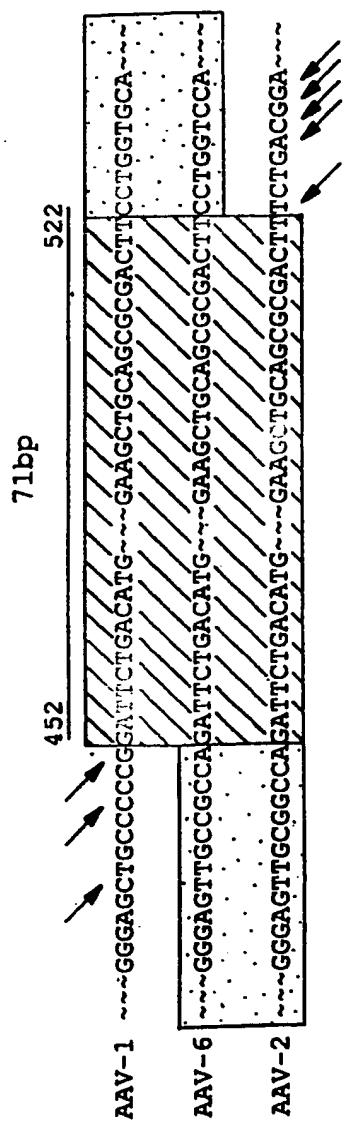


FIG. 3B

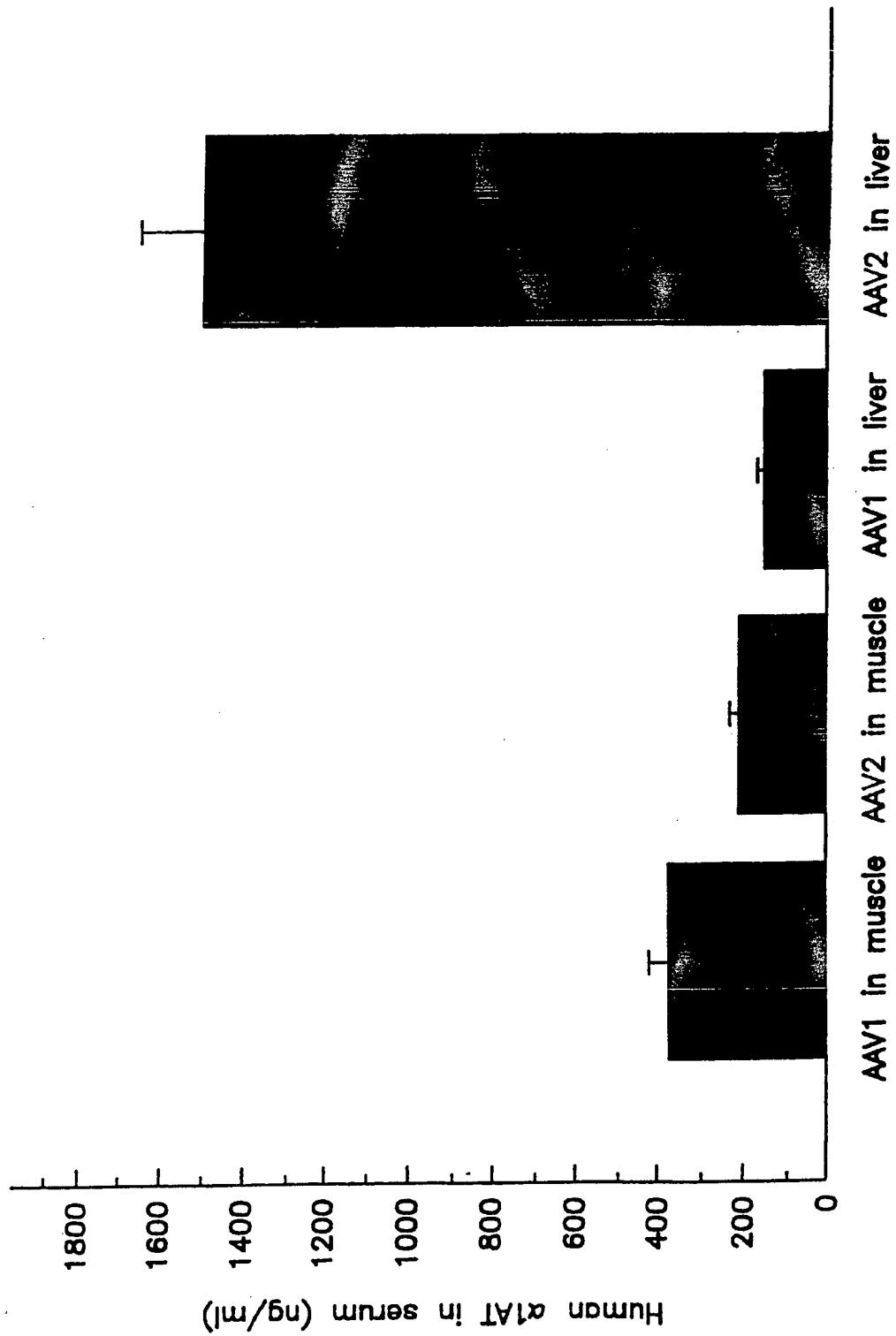


FIG. 4A

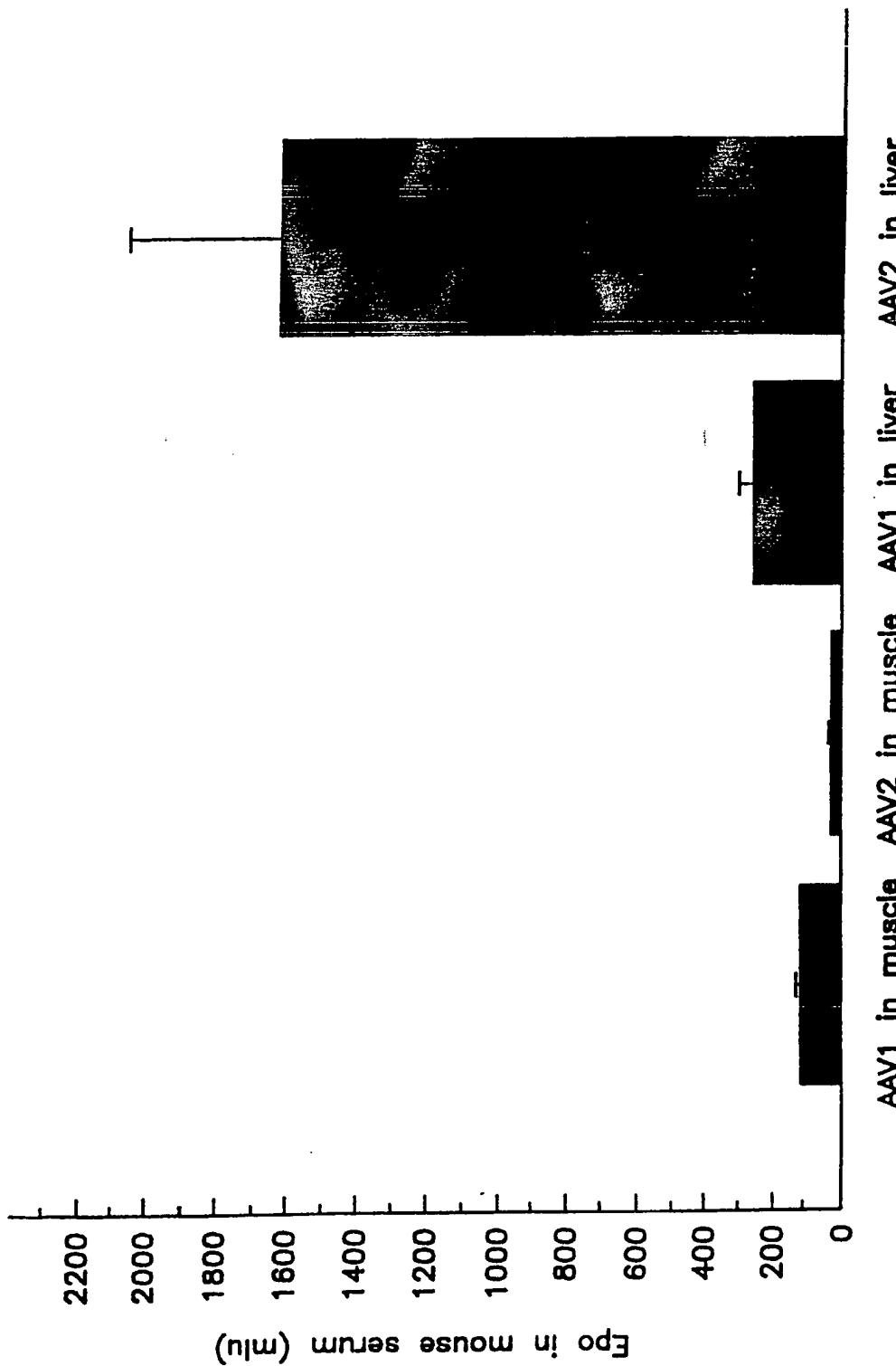


FIG. 4B

FIG. 5A

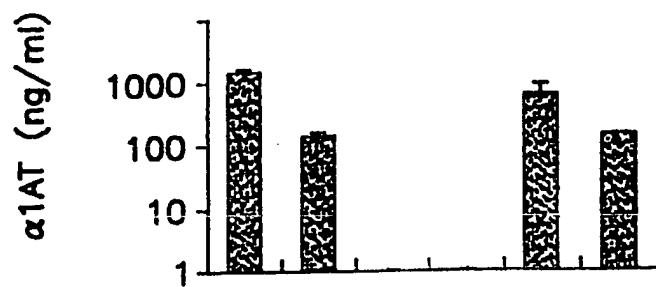


FIG. 5B

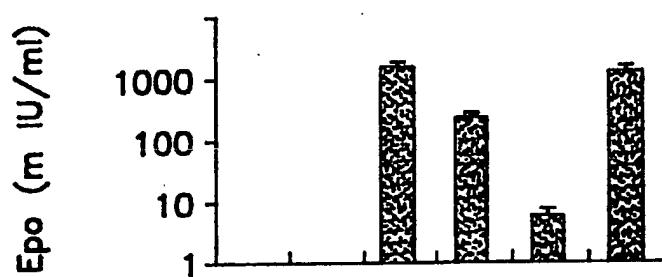


FIG. 5C

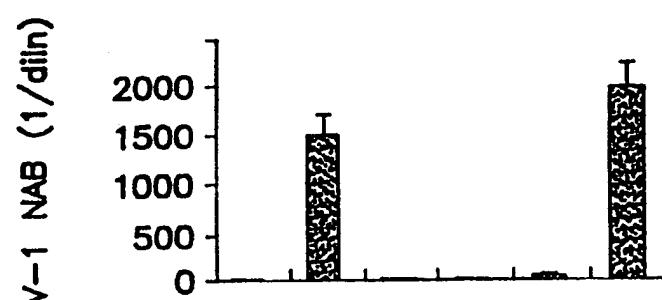
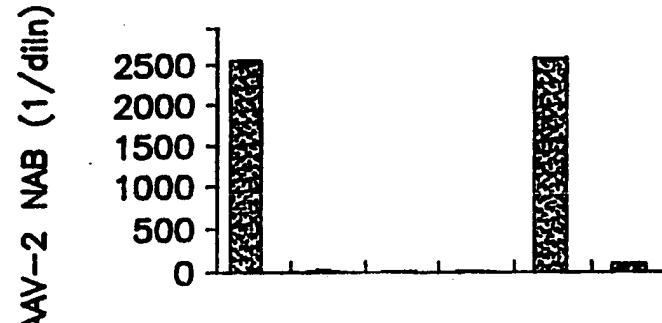


FIG. 5D



Group	1	2	3	4	5	6
Vector1-α1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

FIG. 6A

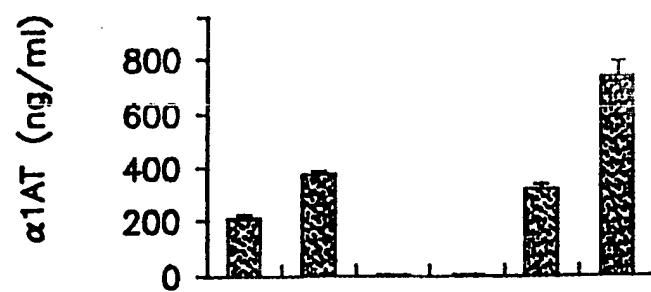


FIG. 6B

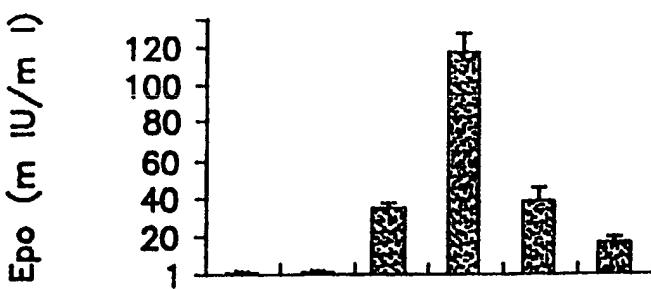


FIG. 6C

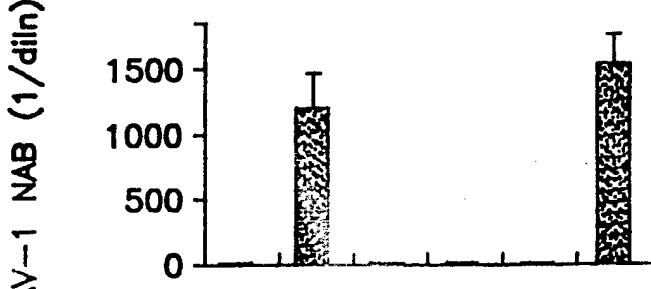
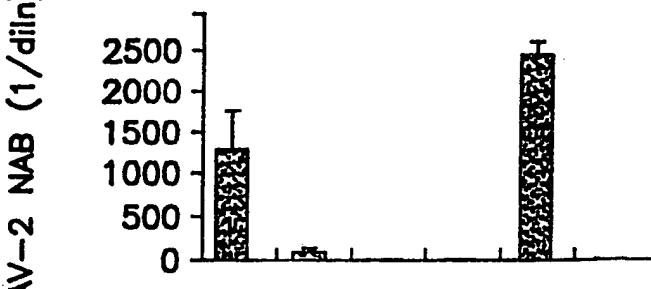


FIG. 6D



Group	1	2	3	4	5	6
Vector1- $\alpha 1AT$	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

SEQUENCE LISTING

<110> Wilson, James M.
Xiao, Weidong
The Trustees of the University of Pennsylvania

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Sequences, Vectors and Host Cells Containing Same

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 Lys Ala Pro Glu Ala Leu Phe Phe Val Gln Phe Glu Lys Gly Glu Ser
 75 80 85

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 Tyr Phe His Leu His Ile Leu Val Glu Thr Thr Gly Val Lys Ser Met
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 Val Leu Gly Arg Phe Leu Ser Gln Ile Arg Asp Lys Leu Val Gln Thr
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 Ile Tyr Arg Gly Ile Glu Pro Thr Leu Pro Asn Trp Phe Ala Val Thr
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 140 145 150

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 155 160 165

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Gln Glu Gln Asn Lys Glu Asn Leu Asn Pro Asn Ser Asp Ala Pro Val			
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atc cgg tca aaa acc tcc gcg cgc tac atg gag ctg gtc ggg tgg ctg	1027		
Ile Arg Ser Lys Thr Ser Ala Arg Tyr Met Glu Leu Val Gly Trp Leu			
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235	240	245	
gcc tcg tac atc tcc ttc aac gcc gct tcc aac tcg cgg tcc cag atc	1123		
Ala Ser Tyr Ile Ser Phe Asn Ala Ala Ser Asn Ser Arg Ser Gln Ile			
250	255	260	
aag gcc gct ctg gac aat gcc ggc aag atc atg gcg ctg acc aaa tcc	1171		
Lys Ala Ala Leu Asp Asn Ala Gly Lys Ile Met Ala Leu Thr Lys Ser			
265	270	275	
gcg ccc gac tac ctg gta ggc ccc gct ccg ccc gcg gac att aaa acc	1219		
Ala Pro Asp Tyr Leu Val Gly Pro Ala Pro Pro Ala Asp Ile Lys Thr			
280	285	290	295
aac cgc atc tac cgc atc ctg gag ctg aac ggc tac gaa cct gcc tac	1267		
Asn Arg Ile Tyr Arg Ile Leu Glu Leu Asn Gly Tyr Glu Pro Ala Tyr			
300	305	310	
gcc ggc tcc gtc ttt ctc ggc tgg gcc cag aaa agg ttc ggg aag cgc	1315		
Ala Gly Ser Val Phe Leu Gly Trp Ala Gln Lys Arg Phe Gly Lys Arg			
315	320	325	
aac acc atc tgg ctg ttt ggg ccg gcc acc acg ggc aag acc aac atc	1363		
Asn Thr Ile Trp Leu Phe Gly Pro Ala Thr Thr Gly Lys Thr Asn Ile			
330	335	340	
gcg gaa gcc atc gcc cac gcc gtg ccc ttc tac ggc tgc gtc aac tgg	1411		
Ala Glu Ala Ile Ala His Ala Val Pro Phe Tyr Gly Cys Val Asn Trp			
345	350	355	
acc aat gag aac ttt ccc ttc aat gat tgc gtc gac aag atg gtg atc	1459		
Thr Asn Glu Asn Phe Pro Phe Asn Asp Cys Val Asp Lys Met Val Ile			
360	365	370	375
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Trp Trp Glu Glu Gly Lys Met Thr Ala Lys Val Val Glu Ser Ala Lys			
380	385	390	

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Ala Ile Leu Gly Gly Ser Lys Val Arg Val Asp Gln Lys Cys Lys Ser			
395	400	405	
tcc gcc cag atc gac ccc acc ccc gtg atc gtc acc tcc aac acc aac	1603		
Ser Ala Gln Ile Asp Pro Thr Pro Val Ile Val Thr Ser Asn Thr Asn			
410	415	420	
atg tgc gcc gtg att gac ggg aac agc acc acc ttc gag cac cag cag	1651		
Met Cys Ala Val Ile Asp Gly Asn Ser Thr Thr Phe Glu His Gln Gln			
425	430	435	
ccg ttg cag gac cgg atg ttc aaa ttt gaa ctc acc cgc cgt ctg gag	1699		
Pro Leu Gln Asp Arg Met Phe Lys Phe Glu Leu Thr Arg Arg Leu Glu			
440	445	450	455
cat gac ttt ggc aag gtg aca aag cag gaa gtc aaa gag ttc ttc cgc	1747		
His Asp Phe Gly Lys Val Thr Lys Gln Glu Val Lys Glu Phe Phe Arg			
460	465	470	
tgg gcg cag gat cac gtg acc gag gtg gcg cat gag ttc tac gtc aga	1795		
Trp Ala Gln Asp His Val Thr Glu Val Ala His Glu Phe Tyr Val Arg			
475	480	485	
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Lys Gly Gly Ala Asn Lys Arg Pro Ala Pro Asp Asp Ala Asp Lys Ser			
490	495	500	
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Glu Pro Lys Arg Ala Cys Pro Ser Val Ala Asp Pro Ser Thr Ser Asp			
505	510	515	
gcg gaa gga gct ccg gtg gac ttt gcc gac agg tac caa aac aaa tgt	1939		
Ala Glu Gly Ala Pro Val Asp Phe Ala Asp Arg Tyr Gln Asn Lys Cys			
520	525	530	535
tct cgt cac gcg ggc atg ctt cag atg ctg ttt ccc tgc aag aca tgc	1987		
Ser Arg His Ala Gly Met Leu Gln Met Leu Phe Pro Cys Lys Thr Cys			
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gag aga atg aat cag aat ttc aac att tgc ttc acg cac ggg acg aga	2035		
Glu Arg Met Asn Gln Asn Phe Asn Ile Cys Phe Thr His Gly Thr Arg			
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Asp Cys Ser Glu Cys Phe Pro Gly Val Ser Glu Ser Gln Pro Val Val			
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acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc tac aag caa Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln 870 875 880	2999
atc tcc agt gct tca acg ggg gcc agc aac gac aac cac tac ttc ggc Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His Tyr Phe Gly 885 890 895	3047
tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc cac tgc cac Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His Cys His 900 905 910 915	3095
ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat tgg gga ttc Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Trp Gly Phe 920 925 930	3143
cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa gtc aag gag Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val Lys Glu 935 940 945	3191
gtc acg acg aat gat ggc gtc aca acc atc gct aat aac ctt acc agc Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn Leu Thr Ser 950 955 960	3239

acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt	ccg tac gtc ctc	3287	
Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu			
965	970	975	
ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg gac gtg ttc		3335	
Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp Val Phe			
980	985	990	995
atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc agc caa gcc		3383	
Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala			
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gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct tct cag atg		3431	
Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met			
1015	1020	1025	
ctg aga acg ggc aac aac ttt acc ttc agc tac acc ttt gag gaa gtg		3479	
Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val			
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cct ttc cac agc agc tac gcg cac agc cag agc ctg gac cgg ctg atg		3527	
Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met			
1045	1050	1055	
aat cct ctc atc gac caa tac ctg tat tac ctg aac aga act caa aat		3575	
Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Leu Asn Arg Thr Gln Asn			
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cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc cgt ggg tct		3623	
Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser			
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cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct gga ccc tgt		3671	
Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys			
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tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac aac aac agc		3719	
Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser			
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aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat ggg cgt gaa		3767	
Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu			
1125	1130	1135	
tcc atc atc aac cct ggc act gct atg gcc tca cac aaa gac gac gaa		3815	
Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys Asp Asp Glu			
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gac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga.aaa gag agc			3863
Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly Lys Glu Ser			
1160	1165	1170	
gcc gga gct tca aac act gca ttg gac aat gtc atg att aca gac gaa			3911
Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile Thr Asp Glu			
1175	1180	1185	
gag gaa att aaa gcc act aac cct gtg gcc acc gaa aga ttt ggg acc			3959
Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg Phe Gly Thr			
1190	1195	1200	
gtg gca gtc aat ttc cag agc agc aca gac cct gcg acc gga gat			4007
Val Ala Val Asn Phe Gln Ser Ser Thr Asp Pro Ala Thr Gly Asp			
1205	1210	1215	
gtg cat gct atg gga gca tta cct ggc atg gtg tgg caa gat aga gac			4055
Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp			
1220	1225	1230	1235
gtg tac ctg cag ggt ccc att tgg gcc aaa att cct cac aca gat gga			4103
Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly			
1240	1245	1250	
cac ttt cac ccg tct cct ctt atg ggc ggc ttt gga ctc aag aac ccg			4151
His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys Asn Pro			
1255	1260	1265	
cct cct cag atc ctc atc aaa aac acg cct gtt cct gcg aat cct ccg			4199
Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn Pro Pro			
1270	1275	1280	
gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc caa tac tcc			4247
Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser			
1285	1290	1295	
aca gga caa gtg agt gtg gaa att gaa tgg gag ctg cag aaa gaa aac			4295
Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn			
1300	1305	1310	1315
agc aag cgc tgg aat ccc gaa gtg cag tac aca tcc aat tat gca aaa			4343
Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys			
1320	1325	1330	
tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt tat act gag			4391
Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu			
1335	1340	1345	

cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg taattacgtg. 4440
 Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
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ttaatcaata aaccgggttga ttcgtttcag ttgaactttg gtctcctgtc cttcttatct 4500
 tatcggttac catggttata ycttacacat taactgcttg gttgcgttc gcgataaaag 4560
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Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly
 130 135 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
145 150 155 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
165 170 175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
195 200 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
210 215 220

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
225 230 235 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
245 250 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
260 265 270

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
275 280 285

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
290 295 300

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
305 310 315 320

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
325 330 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
340 345 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
355 360 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
370 375 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
385 390 395 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
405 410 415

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
420 425 430

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
435 440 445

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
515 520 525

Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
530 535 540

Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
545 550 555 560

Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
565 570 575

Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
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35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145 150 155 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
180 185 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu

245

250

255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
260 265 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
275 280 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
290 295 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
305 310 315 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
325 330 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
340 345 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
355 360 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
370 375 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
385 390 395 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
405 410 415

Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
420 425 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
435 440 445

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
450 455 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
465 470 475 480

Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
485 490 495

Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn

500 505 510

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
515 520 525Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
530 535 540Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile
545 550 555 560Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
565 570 575Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala
580 585 590Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln
595 600 605Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
610 615 620Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
625 630 635 640Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
645 650 655Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
660 665 670Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
675 680 685Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
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 Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
 20 .25 30

aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att 144
 Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg 192
 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt 240
 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag 288
 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att 336
 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
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agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg 384
 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125

ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg 432
 Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
 130 135 140

aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag 480
 Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
 145 150 155 160

act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata 528

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile			
165	170	175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac	576		
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His			
180	185	190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac	624		
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn			
195	200	205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac	672		
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr			
210	215	220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag	720		
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys			
225	230	235	240
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct	768		
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala			
245	250	255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag	816		
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys			
260	265	270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct	864		
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala			
275	280	285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg	912		
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu			
290	295	300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc	960		
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala			
305	310	315	320
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc	1008		
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala			
325	330	335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc	1056		
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro			
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Phe	Tyr	Gly	Cys	Val	Asn	Trp	Thr	Asn	Glu	Asn	Phe	Pro	Phe	Asn	Asp	
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Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala																
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Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg																
385			390			395			400							
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Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val																
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acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt															1344	
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe																
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gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag															1392	
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln																
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485			490			495										
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Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val																
500			505			510										
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc															1584	
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala																
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gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg															1632	
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met																
530			535			540										
ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att															1680	

Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
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 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 565 570 575
 tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1776
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 580 585 590
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 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 595 600 605
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 35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

115	120	125
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly		
130	135	140
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys		
145	150	155
160		
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile		
165	170	175
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His		
180	185	190
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn		
195	200	205
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr		
210	215	220
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys		
225	230	235
240		
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala		
245	250	255
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys		
260	265	270
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala		
275	280	285
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu		
290	295	300
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala		
305	310	315
320		
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala		
325	330	335
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro		
340	345	350
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp		
355	360	365
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala		

370	375	380
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg		
385	390	395
395		
400		
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val		
405	410	415
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser		
420	425	430
430		
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe		
435	440	445
445		
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln		
450	455	460
460		
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val		
465	470	475
475		
480		
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala		
485	490	495
495		
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val		
500	505	510
510		
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala		
515	520	525
525		
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met		
530	535	540
540		
Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile		
545	550	555
555		
560		
Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val		
565	570	575
575		
Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys		
580	585	590
590		
Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala		
595	600	605
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620		

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Met	Pro	Gly	Phe	Tyr	Glu	Ile	Val	Ile	Lys	Val	Pro	Ser	Asp	Leu	Asp	
1	5							10						15		

gag	cac	ctg	ccg	ggc	att	tct	gac	tcg	ttt	gtg	agc	tgg	gtg	gcc	gag	96
Glu	His	Leu	Pro	Gly	Ile	Ser	Asp	Ser	Phe	Val	Ser	Trp	Val	Ala	Glu	
		20						25					30			

aag	gaa	tgg	gag	ctg	ccc	ccg	gat	tct	gac	atg	gat	ctg	aat	ctg	att	144
Lys	Glu	Trp	Glu	Leu	Pro	Pro	Asp	Ser	Asp	Met	Asp	Leu	Asn	Leu	Ile	
		35						40					45			

gag	cag	gca	ccc	ctg	acc	gtg	gcc	gag	aag	ctg	cag	cgc	gac	ttc	ctg	192
Glu	Gln	Ala	Pro	Leu	Thr	Val	Ala	Glu	Lys	Leu	Gln	Arg	Asp	Phe	Leu	
		50				55			60							

gtc	caa	tgg	cgc	cgc	gtg	agt	aag	gcc	ccg	gag	gcc	ctc	ttc	ttt	gtt	240
Val	Gln	Trp	Arg	Arg	Val	Ser	Lys	Ala	Pro	Glu	Ala	Leu	Phe	Phe	Val	
		65			70			75				80				

cag	ttc	gag	aag	ggc	gag	tcc	tac	ttc	cac	ctc	cat	att	ctg	gtg	gag	288
Gln	Phe	Glu	Lys	Gly	Glu	Ser	Tyr	Phe	His	Leu	His	Ile	Leu	Val	Glu	
			85					90				95				

acc	acg	ggg	gtc	aaa	tcc	atg	gtg	ctg	ggc	cgc	ttc	ctg	agt	cag	att	336
Thr	Thr	Gly	Val	Lys	Ser	Met	Val	Leu	Gly	Arg	Phe	Leu	Ser	Gln	Ile	
				100			105					110				

agg	gac	aag	ctg	gtg	cag	acc	atc	tac	cgc	ggg	atc	gag	ccg	acc	ctg	384
Arg	Asp	Lys	Leu	Val	Gln	Thr	Ile	Tyr	Arg	Gly	Ile	Glu	Pro	Thr	Leu	
				115			120				125					

ccc	aac	tgg	ttc	gcg	gtg	acc	aag	acg	cgt	aat	ggc	gcc	gga	ggg	ggg	432
Pro	Asn	Trp	Phe	Ala	Val	Thr	Lys	Thr	Arg	Asn	Gly	Ala	Gly	Gly	Gly	
			130			135			140							

aac	aag	gtg	gtg	gac	gag	tgc	tac	atc	ccc	aac	tac	ctc	ctg	ccc	aag	480
Asn	Lys	Val	Val	Asp	Glu	Cys	Tyr	Ile	Pro	Asn	Tyr	Leu	Leu	Pro	Lys	

145	150	155	160	
act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata 528				
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile				
165	170	175		
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac 576				
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His				
180	185	190		
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac 624				
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn				
195	200	205		
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac 672				
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr				
210	215	220		
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag 720				
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys				
225	230	235	240	
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 768				
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala				
245	250	255		
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 816				
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys				
260	265	270		
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 864				
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala				
275	280	285		
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg 912				
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu				
290	295	300		
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc 960				
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala				
305	310	315	320	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccc gcc 1008				
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala				
325	330	335		
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc 1056				
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro				

340	345	350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat			1104
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp			
355	360	365	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc			1152
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala			
370	375	380	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc			1200
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg			
385	390	395	400
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg			1248
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val			
405	410	415	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc			1296
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser			
420	425	430	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt			1344
Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe			
435	440	445	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag			1392
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln			
450	455	460	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg			1440
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val			
465	470	475	480
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc			1488
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala			
485	490	495	
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc			1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val			
500	505	510	
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc			1584
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala			
515	520	525	
gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa			1632
Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln			

530 535 540

cct ctc tga 1641
Pro Leu
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1 5 10 15Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
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35 40 45Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
50 55 60Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
65 70 75 80Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
85 90 95Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
100 105 110Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
115 120 125Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly
130 135 140Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
145 150 155 160Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
165 170 175Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
195 200 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
210 215 220

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
225 230 235 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
245 250 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
260 265 270

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
275 280 285

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
290 295 300

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
305 310 315 320

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
325 330 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
340 345 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
355 360 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
370 375 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
385 390 395 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
405 410 415

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
420 425 430

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
435 440 445

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
515 520 525

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
530 535 540

Pro Leu
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Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
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cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
20 25 30

tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
35 40 45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
50 55 60

ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg	240
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	
65 70 75 80	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc	288
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	
65 90 95	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccc gcc	336
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	
100 105 110	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc	384
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	
115 120 125	
tcc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat	432
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	
130 135 140	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc	480
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala	
145 150 155 160	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc	528
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg	
165 170 175	
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg	576
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	
180 185 190	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc	624
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	
195 200 205	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt	672
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe	
210 215 220	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag	720
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln	
225 230 235 240	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg	768
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val	
245 250 255	

gct	cat	gat	tcc	tac	gtc	aga	aag	ggt	gga	gcc	aac	aaa	aga	ccc	gcc	816
Ala	His	Glu	Phe	Tyr	Val	Arg	Lys	Gly	Gly	Ala	Asn	Lys	Arg	Pro	Ala	
260					265					270						
ccc	gat	gac	gct	gat	aaa	agc	gag	ccc	aag	cg	gcc	tgc	ccc	tca	g	864
Pro	Asp	Asp	Ala	Asp	Lys	Ser	Glu	Pro	Lys	Arg	Ala	Cys	Pro	Ser	Val	
275					280					285						
gct	gat	cca	tcg	acg	tca	gac	gct	gaa	gga	gct	ccg	gtg	gac	ttt	gcc	912
Ala	Asp	Pro	Ser	Thr	Ser	Asp	Ala	Glu	Gly	Ala	Pro	Val	Asp	Phe	Ala	
290					295					300						
gac	agg	tac	caa	aac	aaa	tgt	tct	cgt	cac	gct	ggc	atg	ctt	cag	atg	960
Asp	Arg	Tyr	Gln	Asn	Lys	Cys	Ser	Arg	His	Ala	Gly	Met	Leu	Gln	Met	
305					310					315			320			
ctg	ttt	ccc	tgc	aag	aca	tgc	gag	aga	atg	aat	cag	aat	ttc	aac	att	1008
Leu	Phe	Pro	Cys	Lys	Thr	Cys	Glu	Arg	Met	Asn	Gln	Asn	Phe	Asn	Ile	
325					330					335						
tgc	tcc	acg	cac	ggg	acg	aga	gac	tgt	tca	gag	tgc	ttc	ccc	ggc	gtg	1056
Cys	Phe	Thr	His	Gly	Thr	Arg	Asp	Cys	Ser	Glu	Cys	Phe	Pro	Gly	Val	
340					345					350						
tca	gaa	tct	caa	ccg	gtc	aga	aag	agg	acg	tat	cgg	aaa	ctc	tgt	1104	
Ser	Glu	Ser	Gln	Pro	Val	Val	Arg	Lys	Arg	Thr	Tyr	Arg	Lys	Leu	Cys	
355					360					365						
gcc	att	cat	cat	ctg	ctg	ggg	cg	gct	ccc	gag	att	gct	tgc	tcg	gcc	1152
Ala	Ile	His	His	Leu	Leu	Gly	Arg	Ala	Pro	Glu	Ile	Ala	Cys	Ser	Ala	
370					375					380						
tgc	gat	ctg	gtc	aac	gt	gac	ctg	gat	gac	tgt	gtt	tct	gag	caa	taa	1200
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20

25

30

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
35 40 45

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
50 55 60

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
65 70 75 80

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
85 90 95

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
100 105 110

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
115 120 125

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
130 135 140

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
145 150 155 160

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
165 170 175

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
180 185 190

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
195 200 205

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
210 215 220

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
225 230 235 240

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
245 250 255

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
260 265 270

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val

275	280	285
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala		
290	295	300
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met		
305	310	315
320		
Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile		
325	330	335
Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val		
340	345	350
Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys		
355	360	365
Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala		
370	375	380
Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln		
385	390	395
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Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys		
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		15
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct		96
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala		
20	25	30
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag		144

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys			
35	40	45	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192			
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala			
50	55	60	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg 240			
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu			
65	70	75	80
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc 288			
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala			
85	90	95	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc 336			
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala			
100	105	110	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc 384			
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro			
115	120	125	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat 432			
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp			
130	135	140	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc 480			
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala			
145	150	155	160
aag gtc gng gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc 528			
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg			
165	170	175	
gtg gac caa aag tgc aag tcc gcc cag atc gac ccc acc ccc gtg 576			
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val			
180	185	190	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc 624			
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser			
195	200	205	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt 672			
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe			
210	215	220	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag 720			

Glu	Leu	Thr	Arg	Arg	Leu	Glu	His	Asp	Phe	Gly	Lys	Val	Thr	Lys	Gln	
225					230				235			240				
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg															768	
Glu	Val	Lys	Glu	Phe	Phe	Arg	Trp	Ala	Gln	Asp	His	Val	Thr	Glu	Val	
					245				250			255				
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc															816	
Ala	His	Glu	Phe	Tyr	Val	Arg	Lys	Gly	Gly	Ala	Asn	Lys	Arg	Pro	Ala	
					260				265			270				
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc															864	
Pro	Asp	Asp	Ala	Asp	Lys	Ser	Glu	Pro	Lys	Arg	Ala	Cys	Pro	Ser	Val	
					275				280			285				
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc															912	
Ala	Asp	Pro	Ser	Thr	Ser	Asp	Ala	Glu	Gly	Ala	Pro	Val	Asp	Phe	Ala	
					290				295			300				
gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa															960	
Asp	Arg	Tyr	Gly	Cys	Arg	Trp	Leu	Ser	Ser	Arg	Leu	Ala	Arg	Gly	Gln	
					305				310			315			320	
cct ctc tga															969	
Pro	Leu															
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1					5				10			15				
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala																
					20				25			30				
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys																
					35				40			45				
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala																
					50				55			60				
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu																
					65				70			75			80	

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
85 90 95

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
100 105 110

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
115 120 125

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
130 135 140

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
145 150 155 160

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
165 170 175

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
180 185 190

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
195 200 205

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
210 215 220

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
225 230 235 240

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
245 250 255

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
260 265 270

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
275 280 285

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
290 295 300

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
305 310 315 320

Pro Leu

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 Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
 1 5 10 15
 gag ggc att cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc 96
 Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
 20 25 30
 aaa gcc aac cag caa aag cag gac gac ggc ccg ggt ctg gtg ctt cct 144
 Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
 35 40 45
 ggc tac aag tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc 192
 Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60
 gtc aac gcg gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac 240
 Val Asn Ala Ala Asp Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80
 cag cag ctc aaa gcg ggt gac aat ccg tac ctg ccg tat aac cac gcc 288
 Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95
 gac gcc gag ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc 336
 Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110
 aac ctc ggg cga gca gtc ttc cag gcc aag aag ccg gtt ctc gaa cct 384
 Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125
 ctc ggt ctg gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt 432
 Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140
 ccg gta gag cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc 480

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly			
145	150	155	160
aag aca ggc cag cag ccc gct aaa aag aga ctc aat ttt ggt cag act	528		
Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr			
165	170	175	
ggc gac tca gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca	576		
Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro			
180	185	190	
gca acc ccc gct gct gtg gga cct act aca atg gct tca ggc ggt ggc	624		
Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly			
195	200	205	
gca cca atg gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc	672		
Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala			
210	215	220	
tca gga aat tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc	720		
Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile			
225	230	235	240
acc acc agc acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc	768		
Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu			
245	250	255	
tac aag caa atc tcc agt gct tca acg ggg gcc agc aac gac aac cac	816		
Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His			
260	265	270	
tac ttc ggc tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc	864		
Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe			
275	280	285	
cac tgc cac ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat	912		
His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn			
290	295	300	
tgg gga ttc cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa	960		
Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln			
305	310	315	320
gtc aag gag gtc acg acg aat gat ggc gtc aca acc atc gct aat aac	1008		
Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn			
325	330	335	
ctt acc agc acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg	1056		

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro				
340	345	350		
tac gtc ctc ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg				1104
Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala				
355	360	365		
gac gtg ttc atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc				1152
Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly				
370	375	380		
agc caa gcc gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct				1200
Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro				
385	390	395	400	
tct cag atg ctg aga acg ggc aac aac ttt acc ttc agc tac acc ttt				1248
Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe				
405	410	415		
gag gaa gtg cct ttc cac agc agc tac gcg cac agc cag agc ctg gac				1296
Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp				
420	425	430		
cggttgatg aat cct ctc atc gac caa tac ctg tat tac ctg aac aga				1344
Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg				
435	440	445		
act caa aat cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc				1392
Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser				
450	455	460		
cggtggatc cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct				1440
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro				
465	470	475	480	
ggatccc ttt tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac				1488
Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn				
485	490	495		
aac aac agc aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat				1536
Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn				
500	505	510		
ggatcgatg gaa tcc atc atc aac cct ggc act gct atg gcc tca cac aaa				1584
Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys				
515	520	525		
qac qac qaa qac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga				1632

Asp	Asp	Glu	Asp	Lys	Phe	Phe	Pro	Met	Ser	Gly	Val	Met	Ile	Phe	Gly	
530					535			540								
aaa gag agc gcc gga gct tca aac act gca ttg gac aat gtc atg att															1680	
Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile																
545		550		555		560										
aca gag gaa gag gaa att aac gcc act aac cct gtg gcc acc gaa aga															1728	
Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg																
565		570		575												
ttt ggg acc gtg gca gtc aat ttc cag agc agc aca gac cct gcg															1776	
Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala																
580		585		590												
acc gga gat gtg cat gct atg gga gca tta cct ggc atg gtg tgg caa															1824	
Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln																
595		600		605												
gat aga gac gtg tac ctg cag ggt ccc att tgg gcc aaa att cct cac															1872	
Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His																
610		615		620												
aca gat gga cac ttt cac ccc tct ctt atg ggc ggc ttt gga ctc															1920	
Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu																
625		630		635		640										
aag aac ccg cct ctc cag atc ctc atc aaa aac acg cct gtt cct gcg															1968	
Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala																
645		650		655												
aat cct ccg gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc															2016	
Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr																
660		665		670												
caa tac tcc aca gga caa gtg agt gtg gaa att gaa tgg gag ctg cag															2064	
Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln																
675		680		685												
aaa gaa aac agc aag cgc tgg aat ccc gaa gtg cag tac aca tcc aat															2112	
Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn																
690		695		700												
tat gca aaa tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt															2160	
Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu																
705		710		715		720										
tat act gag cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg															2208	

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
725 730 735

taa

2211

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<400> 13

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20 25 30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145 150 155 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
180 185 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
245 250 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
260 265 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
275 280 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
290 295 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
305 310 315 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
325 330 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
340 345 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
355 360 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
370 375 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
385 390 395 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
405 410 415

Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
420 425 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
435 440 445

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
450 455 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
465 470 475 480

Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
485 490 495

Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
500 505 510

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
515 520 525

Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
530 535 540

Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile
545 550 555 560

Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
565 570 575

Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala
580 585 590

Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln
595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
610 615 620

Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
625 630 635 640

Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
645 650 655

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
660 665 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
690 695 700

Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu
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Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
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gac tcc tcc tcg ggc atc ggc aag aca ggc cag cag ccc gct aaa aag 96
 Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly Gln Gln Pro Ala Lys Lys
 20 25 30

aga ctc aat ttt ggt cag act ggc gac tca gag tca gtc ccc gat cca 144
 Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro
 35 40 45

caa cct ctc gga gaa cct cca gca acc ccc gct gct gtg gga cct act 192
 Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
 50 55 60

aca atg gct tca ggc ggt ggc gca cca atg gca gac aat aac gaa ggc 240
 Thr Met Ala Ser Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
 65 70 75 80

gcc gac gga gtg ggt aat gcc tca gga aat tgg cat tgc gat tcc aca 288
 Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr
 85 90 95

tgg ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg 336
 Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu
 100 105 110

ccc acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg 384
 Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr
 115 120 125

ggg gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg 432
 Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
 130 135 140

tat ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg 480
 Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
 145 150 155 160

cag cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac 528
 Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
 165 170 175

ttc aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc 576
 Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
 180 185 190

gtc aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg 624
 Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
 195 200 205

gac tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc 672
 Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
 210 215 220

tgc ctc cct ccg ttc ccg gcg gac gtg ttc atg att ccg caa tac ggc 720
 Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
 225 230 235 240

tac ctg acg ctc aac aat ggc agc caa gcc gtg gga cgt tca tcc ttt 768
 Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
 245 250 255

tac tgc ctg gaa tat ttc cct tct cag atg ctg aga acg ggc aac aac 816
 Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
 260 265 270

ttt acc ttc agc tac acc ttt gag gaa gtg cct ttc cac agc acg tac 864
 Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr
 275 280 285

gcg cac agc cag agc ctg gac ccg ctg atg aat cct ctc atc gac caa 912
 Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
 290 295 300

tac ctg tat tac ctg aac aga act gaa aat cag tcc gga agt gcc caa 960
 Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
 305 310 315 320

aac aag gac ttg ctg ttt agc cgt ggg tct cca gct gyc atg tct gtt		1008	
Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val			
325	330	335	
cag ccc aaa aac tgg cta cct gga ccc tgt tat cgg cag cag cgc gtt		1056	
Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val			
340	345	350	
tct aaa aca aaa aca gac aac aac agc aat ttt acc tgg act ggt		1104	
Ser Lys Thr Lys Thr Asp Asn Asn Ser Asn Phe Thr Trp Thr Gly			
355	360	365	
gct tca aaa tat aac ctc aat ggg cgt gaa tcc atc atc aac cct ggc		1152	
Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly			
370	375	380	
act gct atg gcc tca cac aaa gac gac gaa gac aag ttc ttt ccc atg		1200	
Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met			
385	390	395	400
agc ggt gtc atg att ttt gga aaa gag agc gcc gga gct tca aac act		1248	
Ser Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr			
405	410	415	
gca ttg gac aat gtc atg att aca gac gaa gag gaa att aaa gcc act		1296	
Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Ile Lys Ala Thr			
420	425	430	
aac cct gtg gcc acc gaa aga ttt ggg acc gtg gca gtc aat ttc cag		1344	
Asn Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln			
435	440	445	
agc agc agc aca gac cct gcg acc gga gat gtg cat gct atg gga gca		1392	
Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala			
450	455	460	
tta cct ggc atg gtg tgg caa gat aga gac gtg tac ctg cag ggt ccc		1440	
Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro			
465	470	475	480
att tgg gcc aaa att cct cac aca gat gga cac ttt cac ccg tct cct		1488	
Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro			
485	490	495	
ctt atg ggc ggc ttt gga ctc aag aac ccg cct cct cag atc ctc atc		1536	
Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile			
500	505	510	

aaa aac acg cct gtt cct gcg aat cct ccg gcg gag ttt tca gct aca	1584
Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr	
515 520 525	
aag ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg	1632
Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val	
530 535 540	
gaa att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc	1680
Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro	
545 550 555 560	
gaa gtg cag tac aca tcc aat tat gcg aaa tct gcc aac gtt gat ttt	1728
Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe	
565 570 575	
act gtg gac aac aat gga ctt tat act gag cct cgc ccc att ggc acc	1776
Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr	
580 585 590	
cgt tac ctt acc cgt ccc ctg taa	1800
Arg Tyr Leu Thr Arg Pro Leu	
595	
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Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly Gln Gln Pro Ala Lys Lys	
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Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro	
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Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr	
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Thr Met Ala Ser Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly	
65 70 75 80	
Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr	

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90

95

Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu
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Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr
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Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
130 135 140

Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
145 150 155 160

Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
165 170 175

Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
180 185 190

Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
195 200 205

Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
210 215 220

Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
225 230 235 240

Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
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Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
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Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val
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Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val

340

345

350

Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly
355 360 365

Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly
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Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met
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435 440 445

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450 455 460

Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro
465 470 475 480

Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro
485 490 495

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500 505 510

Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr
515 520 525

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Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
545 550 555 560

Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe
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Asp	Gly	Val	Gly	Asn	Ala	Ser	Gly	Asn	Trp	His	Cys	Asp	Ser	Thr	Trp	
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ctg	ggc	gac	aga	gtc	atc	acc	acc	agc	acc	cgc	acc	tgg	gcc	ttg	ccc	144
Leu	Gly	Asp	Arg	Val	Ile	Thr	Thr	Ser	Thr	Arg	Thr	Trp	Ala	Leu	Pro	
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acc	tac	aat	aac	cac	ctc	tac	aag	caa	atc	tcc	agt	gct	tca	acg	ggg	192
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Phe	Asp	Phe	Asn	Arg	Phe	His	Cys	His	Phe	Ser	Pro	Arg	Asp	Trp	Gln	
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cga	ctc	atc	aac	aac	aat	tgg	gga	ttc	cg	ccc	aag	aga	ctc	aac	ttc	336
Arg	Leu	Ile	Asn	Asn	Asn	Trp	Gly	Phe	Arg	Pro	Lys	Arg	Leu	Asn	Phe	
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Lys	Leu	Phe	Asn	Ile	Gln	Val	Lys	Glu	Val	Thr	Thr	Asn	Asp	Gly	Val		
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aca	acc	atc	gct	aat	aac	ctt	acc	agc	acg	gtt	caa	gtc	ttc	tgc	gac	432
Thr	Thr	Ile	Ala	Asn	Asn	Leu	Thr	Ser	Thr	Val	Gln	Val	Phe	Ser	Asp	
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Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr	
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Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe	
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acc ttc agc tac acc ttt gag gaa gtg cct ttc cac agc agc tac gcg	672
Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala	
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His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr	
225 230 235 240	
ctg tat tac ctg aac aga act caa aat cag tcc gga agt gcc caa aac	768
Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Ser Gly Ser Ala Gln Asn	
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Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln	
260 265 270	
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Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser	
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Lys Thr Lys Thr Asp Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala	
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Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr	
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 Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
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tgg gcc aaa att cct cac aca gat gga cac ttt cac ccg tct cct ctt 1296
 Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
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 Met Gly Phe Gly Leu Lys Asn Pro Pro Gln Ile Leu Ile Lys
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 Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys
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ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg gaa 1440
 Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu
 465 470 475 480

att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc gaa 1488
 Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu
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gtg cag tac aca tcc aat tat gca aaa tct gcc aac gtt gat ttt act 1536
 Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr
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1605

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Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly
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Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
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Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
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Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
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Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
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Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp
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Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys
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Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr
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Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr
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Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe
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Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala
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His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr
225 230 235 240

Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn
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Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln
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Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser
275 280 285

Lys Thr Lys Thr Asp Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala
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Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr
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Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met Ser
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Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala
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Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn
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Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln Ser
370 375 380

Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala Leu
385 390 395 400

Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
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Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
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Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys
435 440 445

Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys
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Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu
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Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu
485 490 495

Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr
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4681

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